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     (FILE 'HOME' ENTERED AT 17:45:59 ON 20 JUN 2006)

     FILE 'CAPLUS, MEDLINE' ENTERED AT 17:46:10 ON 20 JUN 2006
L1             0 S TUMOR? (P) HYALURON? (P) ?BENZYL? (P) CROSS?
L2             0 S TUMOUR? (P) HYALURON? (P) ?BENZYL? (P) CROSS?
L3             2 S TUMOR? (P) HYALURON? (P) ?BENZYL?
L4           154 S TUMOR? (P) HYALURON? (P) ?ESTER?
L5             8 S TUMOR? (P) HYALURON? (P) ?ESTER? (P) CROSS?
L6            13 S TUMOR? (P) HYALURON? (P) ?ESTER? (P) SURG?
L7           141 S L4 NOT L6
L8           135 S L7 NOT L5
L9             1 S L8 AND CAVIT?
L10            2 S L8 AND ?CARBOXY?
L11            1 S L8 AND ?EXCISION?
L12            2 S L8 AND REMOVAL?
L13           11 S L8 AND DERIVAT?
L14            0 S L8 AND FILLING?
L15            0 S L8 AND FILL?
L16            0 S L8 AND FILLED?
L17           20 S L8 AND PRIMAR?
L18            5 S L8 AND SECONDAR?
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L3 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:694981 CAPLUS
DOCUMENT NUMBER: 143:482971
TITLE: Implantation of preadipocyte-loaded hyaluronic acid-based scaffolds into nude mice to evaluate potential for soft tissue engineering
AUTHOR(S): Hemmrich, Karsten; von Heimburg, Dennis; Rendchen, Raoul; Di Bartolo, Chiara; Milella, Eva; Pallua, Norbert
CORPORATE SOURCE: Department of Plastic Surgery and Hand Surgery, University Hospital of the Aachen University of Technology, Aachen, D-52057, Germany
SOURCE: Biomaterials (2005), 26(34), 7025-7037
CODEN: BIMADU; ISSN: 0142-9612
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The reconstruction of soft tissue defects following extensive deep burns or **tumor** resections remains an unresolved problem in plastic and reconstructive surgery since adequate implant materials are still not available. Preadipocytes, immature precursor cells found between mature adipocytes in adipose tissue, are a potential material for soft tissue engineering since they can proliferate and differentiate into adipose tissue after transplantation. In previous studies, the authors identified **hyaluronan benzyl** ester (HYAFF-11) sponges to be promising carrier matrixes. This study now evaluates, in vitro and in vivo, a new sponge architecture with pores of 400 μm either made of plain HYAFF-11 or HYAFF-11 coated with the extracellular matrix glycosaminoglycan **hyaluronic** acid. Human preadipocytes were isolated, seeded onto carriers and implanted into nude athymic mice. Explants harvested after 3, 8, and 12 wk were examined for macroscopical appearance, thickness, weight, pore structure, histol., and immunohistochem. Compared to previous studies, the authors found better penetration of cells into both types of scaffolds, with more extensive formation of new vessels throughout the construct but with only minor adipose tissue. The authors' encouraging results contribute towards a better seeded and vascularized scaffold but also show that the enhancement of adipogenic conversion of preadipocytes remains a major task for further in vivo expts.
REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2005400405 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15964623
TITLE: Implantation of preadipocyte-loaded hyaluronic acid-based scaffolds into nude mice to evaluate potential for soft tissue engineering.
AUTHOR: Hemmrich Karsten; von Heimburg Dennis; Rendchen Raoul; Di Bartolo Chiara; Milella Eva; Pallua Norbert
CORPORATE SOURCE: Department of Plastic Surgery and Hand Surgery, Burn Centre, University Hospital of the Aachen University of Technology, Germany.
SOURCE: Biomaterials, (2005 Dec) Vol. 26, No. 34, pp. 7025-37. Journal code: 8100316. ISSN: 0142-9612.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: (EVALUATION STUDIES) Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 3 Aug 2005
Last Updated on STN: 15 Dec 2005

Entered Medline: 7 Dec 2005

AB The reconstruction of soft tissue defects following extensive deep burns or **tumor** resections remains an unresolved problem in plastic and reconstructive surgery since adequate implant materials are still not available. Preadipocytes, immature precursor cells found between mature adipocytes in adipose tissue, are a potential material for soft tissue engineering since they can proliferate and differentiate into adipose tissue after transplantation. In previous studies, we identified **hyaluronan benzyl** ester (HYAFF 11) sponges to be promising carrier matrices. This study now evaluates, in vitro and in vivo, a new sponge architecture with pores of 400 microm either made of plain HYAFF 11 or HYAFF 11 coated with the extracellular matrix glycosaminoglycan **hyaluronic** acid. Human preadipocytes were isolated, seeded onto carriers and implanted into nude athymic mice. Explants harvested after 3, 8, and 12 weeks were examined for macroscopical appearance, thickness, weight, pore structure, histology, and immunohistochemistry. Compared to previous studies, we found better penetration of cells into both types of scaffolds, with more extensive formation of new vessels throughout the construct but with only minor adipose tissue. Our encouraging results contribute towards a better seeded and vascularised scaffold but also show that the enhancement of adipogenic conversion of preadipocytes remains a major task for further in vivo experiments.

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1177959 CAPLUS
DOCUMENT NUMBER: 143:446858
TITLE: Hyaluronic acid based copolymers
INVENTOR(S): Hossainy, Syed Faiyaz Ahmed; Michal, Eugene; Glauser, Thierry; Kwok, Connie; Pacetti, Stephen Dirk
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 11 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005244363	A1	20051103	US 2004-835912	20040430
WO 2005110505	A2	20051124	WO 2005-US14614	20050427

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2004-835912 A 20040430
AB **Hyaluronic** acid (HA) conjugates or **crosslinked** HAs compns. for coating an implantable device are provided. The implantable device can be used for treating a disorder such as atherosclerosis, thrombosis, restenosis, high **cholesterol**, hemorrhage, vascular dissection or perforation, vascular aneurysm, vulnerable plaque, chronic total occlusion, claudication, anastomotic proliferation for vein and artificial grafts, bile duct obstruction, ureter obstruction, **tumor** obstruction, and combinations thereof.

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:248089 CAPLUS
DOCUMENT NUMBER: 142:443764
TITLE: The TSG-6 and IαI Interaction Promotes a Transesterification Cleaving the Protein-Glycosaminoglycan-Protein (PGP) Cross-link
AUTHOR(S): Sanggaard, Kristian W.; Karring, Henrik; Valnickova, Zuzana; Thogersen, Ida B.; Enghild, Jan J.
CORPORATE SOURCE: Center for Insoluble Protein Structure, Department of Molecular Biology, University of Aarhus, Aarhus C, DK-8000, Den.
SOURCE: Journal of Biological Chemistry (2005), 280(12), 11936-11942
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB During co-incubation of human inter-α-inhibitor (IαI) and human **tumor** necrosis factor-stimulated gene 6 protein (TSG-6) SDS-stable interactions are formed between the two proteins. We have analyzed the products of this reaction and characterized the mechanism of complex formation. Following the incubation seven new bands not

previously identified were apparent in SDS-PAGE. Three of these bands did not contain TSG-6, including heavy chain (HC)1·bikunin, HC2·bikunin, and free bikunin. In addition high mol. weight complexes composed of the same components as IαI, including HC1, HC2, and bikunin, were formed. The formation of these complexes was prevented by the addition of **hyaluronan**. The **crosslinks** stabilizing these complexes display properties similar to the protein-glycosaminoglycan-protein (PGP) **crosslink**. The TSG-6-containing SDS-stable complexes were composed of HC1·TSG-6 or HC2·TSG-6 exclusively. Both glycosylated and non-glycosylated TSG-6 participated in the complex formation. The HC·TSG-6 **crosslinks** were different from the PGP **crosslink** and were determined to be **ester** bonds between the α-carbonyl of the C-terminal Asp of the heavy chain and most likely a hydroxyl group containing the TSG-6 residue. The mechanism involved cleaving the PGP **crosslink** of IαI during a **transesterification** reaction. A TSG-6 hydroxyl group reacts with the **ester** bond between the α-carbonyl of the C-terminal Asp residues of HC1 or HC2 and carbon-6 of an internal N-acetylgalactosamine of the chondroitin-4-sulfate chain. An intermediate is formed resulting in a partitioning of the reaction between HC(1 or 2)·TSG-6 complexes and transfer of HC(1 or 2) to the chondroitin via competing pathways.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2001:471288 CAPLUS

DOCUMENT NUMBER: 135:178485

TITLE: TSG-6 is concentrated in the extracellular matrix of mouse cumulus oocyte complexes through hyaluronan and inter-alpha-inhibitor binding

AUTHOR(S): Carrette, Odile; Nemade, Rashmi V.; Day, Anthony J.; Brickner, Amanda; Larsen, William J.

CORPORATE SOURCE: Department of Cell Biology, Neurobiology and Anatomy, Vontz Center for Molecular Studies, University of Cincinnati, Cincinnati, OH, 45267-0521, USA

SOURCE: Biology of Reproduction (2001), 65(1), 301-308
CODEN: BIREBV; ISSN: 0006-3363

PUBLISHER: Society for the Study of Reproduction

DOCUMENT TYPE: Journal

LANGUAGE: English

AB During development of ovarian follicles in mammals, cumulus cells and the oocyte form a mucoelastic mass that detaches itself from peripheral granulosa cell layers upon an ovulatory surge. The integrity of this cumulus-oocyte complex (COC) relies on the cohesiveness of a **hyaluronan** (HA)-enriched extracellular matrix (ECM). We previously identified a serum glycoprotein, inter-alpha-inhibitor (IαI), that is critical in organizing and stabilizing this matrix. Following an ovulatory stimulus, IαI diffuses into the follicular fluid and becomes integrated in the ECM through its association with HA. TSG-6 (the secreted product of the **tumor** necrosis factor-stimulated gene 6), another HA binding protein, forms a complex with IαI in synovial fluid. The purpose of this study was to investigate whether TSG-6 is involved in the ECM organization of COCs. Immunolocalization of TSG-6 and IαI in mouse COCs at different ovulatory stages was analyzed by immunofluorescence and laser confocal microscopy. IαI, TSG-6, and HA colocalized in the cumulus ECM. **Western** blot analyses were consistent with the presence of both TSG-6 and TSG-6/IαI complexes in ovulated COCs. These results suggest that TSG-6 has a structural role in COC matrix formation possibly mediating **crosslinking** of sep. HA mols. through its binding to IαI.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2001:383876 CAPLUS
DOCUMENT NUMBER: 135:17466
TITLE: Differential expression of CD44 isoforms during liver regeneration in rats
AUTHOR(S): Della Fazia, Maria Agnese; Pettirossi, Valentina; Ayroldi, Emira; Riccardi, Carlo; Magni, Mariapia Viola; Servillo, Giuseppe
CORPORATE SOURCE: Dipartimento di Scienze Biochimiche e di Biotecnologie Molecolari, Sezione di Fisiopatologia, Universita di Perugia, Perugia, 06100, Italy
SOURCE: Journal of Hepatology (2001), 34(4), 555-561
CODEN: JOHEEC; ISSN: 0168-8278
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antigen CD44 is a transmembrane glycoprotein known to bind **hyaluronic** acid (HA). This mol. is a multifunctional cell surface glycoprotein involved in lymphocyte homing and activation, **tumor** growth, and metastasis. Here, the authors investigated the qual. modification of CD44 in the regenerating liver as a model for studying cellular proliferation in vivo. Mols. involved in cell adhesion and the extracellular matrix (ECM), which influence differentiation, growth, cell-cell interactions, and cellular polarity, play an important role in the liver regeneration. The authors studied the modulation of CD44 gene expression and its post-transcriptional modifications, analyzing the expression of different isoforms containing exon v6 in the regenerating liver, in sham-operated liver and in hepatoma H-35 cells. The expression of CD44 and CD44v6 were analyzed in RNA extracted from regenerating liver at different times after partial hepatectomy (PH), and in H-35 hepatoma cells by Northern blot, RT-PCR and Southern blot, and in protein exts. from regenerating liver by **Western** blot. H-35 hepatoma cells were assayed with the antibody **crosslinked** technique with CD44 antibodies. The standard CD44 form was expressed in regenerating liver and its levels were not modified following PH. However, the anal. revealed CD44 isoforms containing v6 in the 1st hours after PH as well as in the H-35 hepatoma cell line. H-35 cells treated with **crosslinked** anti-CD44 antibodies or HA showed an increased rate of incorporation of [3H]thymidine (30 and 25%, resp.) with respect to the control. These findings suggest that CD44 may play a role in the proliferation of residual hepatocytes following PH.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2005146229 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15653696
TITLE: The TSG-6 and I alpha I interaction promotes a transesterification cleaving the protein-glycosaminoglycan-protein (PGP) cross-link.
AUTHOR: Sanggaard Kristian W; Karring Henrik; Valnickova Zuzana; Thogersen Ida B; Enghild Jan J
CORPORATE SOURCE: Center for Insoluble Protein Structure at the Department of Molecular Biology, University of Aarhus, DK-8000 Aarhus C, Denmark.
SOURCE: The Journal of biological chemistry, (2005 Mar 25) Vol. 280, No. 12, pp. 11936-42. Electronic Publication: 2005-01-14.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 200504
ENTRY DATE: Entered STN: 22 Mar 2005
Last Updated on STN: 22 Apr 2005
Entered Medline: 21 Apr 2005

AB During co-incubation of human inter-alpha-inhibitor (IalphaI) and human **tumor** necrosis factor-stimulated gene 6 protein (TSG-6) SDS-stable interactions are formed between the two proteins. We have analyzed the products of this reaction and characterized the mechanism of complex formation. Following the incubation seven new bands not previously identified were apparent in SDS-PAGE. Three of these bands did not contain TSG-6, including heavy chain (HC)1.bikunin, HC2.bikunin, and free bikunin. In addition high molecular weight complexes composed of the same components as I alpha I, including HC1, HC2, and bikunin, were formed. The formation of these complexes was prevented by the addition of **hyaluronan**. The **cross**-links stabilizing these complexes displaying properties similar to the protein-glycosaminoglycan-protein (PGP) **cross**-link. The TSG-6-containing SDS-stable complexes were composed of HC1.TSG-6 or HC2.TSG-6 exclusively. Both glycosylated and non-glycosylated TSG-6 participated in the complex formation. The HC.TSG-6 **cross**-links were different from the PGP **cross** -link and were determined to be **ester** bonds between the alpha-carbonyl of the C-terminal Asp of the heavy chain and most likely a hydroxyl group containing the TSG-6 residue. The mechanism involved cleaving the PGP **cross**-link of I alpha I during a **transesterification** reaction. A TSG-6 hydroxyl group reacts with the **ester** bond between the alpha-carbonyl of the C-terminal Asp residues of HC1 or HC2 and carbon-6 of an internal N-acetylgalactosamine of the chondroitin-4-sulfate chain. An intermediate is formed resulting in a partitioning of the reaction between HC(1 or 2).TSG-6 complexes and transfer of HC(1 or 2) to the chondroitin via competing pathways.

L5 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2001683974 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11729749
TITLE: Cooperation of liver cells in health and disease.
AUTHOR: Kmiec Z
CORPORATE SOURCE: Medical University of Gdansk, Department of Histology and Immunology, 80211 Gdansk, Poland.. zkmiec@amg.gda.pl
SOURCE: Advances in anatomy, embryology, and cell biology, (2001) Vol. 161, pp. III-XIII, 1-151. Ref: 724
Journal code: 0407712. ISSN: 0301-5556.
PUB. COUNTRY: Germany: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 4 Dec 2001
Last Updated on STN: 24 Jan 2002
Entered Medline: 31 Dec 2001

AB The liver lobule is formed by parenchymal cells, i.e., hepatocytes and nonparenchymal cells. In contrast to hepatocytes that occupy almost 80% of the total liver volume and perform the majority of numerous liver functions, nonparenchymal liver cells, which contribute only 6.5% to the liver volume, but 40% to the total number of liver cells, are localized in the sinusoidal compartment of the tissue. The walls of hepatic sinusoid are lined by three different cell types: sinusoidal endothelial cells (SEC), Kupffer cells (KC), and hepatic stellate cells (HSC, formerly known as fat-storing cells, Ito cells, lipocytes, perisinusoidal cells, or vitamin A-rich cells). Additionally, intrahepatic lymphocytes (IHL), including pit cells, i.e., liver-specific natural killer cells, are often present in the sinusoidal lumen. It has been increasingly recognized that both under normal and pathological conditions, many hepatocyte functions are regulated by substances released from neighboring nonparenchymal

cells. Liver sinusoidal endothelial cells constitute the lining or wall of the hepatic sinusoid. They perform important filtration function due to the presence of small fenestrations that allow free diffusion of many substances, but not of particles of the size of chylomicrons, between the blood and the hepatocyte surface. SEC show huge endocytic capacity for many ligands including glycoproteins, components of the extracellular matrix (ECM; such as **hyaluronate**, collagen fragments, fibronectin, or chondroitin sulphate proteoglycan), immune complexes, transferrin and ceruloplasmin. SEC may function as antigen-presenting cells (APC) in the context of both MHC-I and MHC-II restriction with the resulting development of antigen-specific T-cell tolerance. They are also active in the secretion of cytokines, eicosanoids (i.e., prostanoids and leukotrienes), endothelin-1, nitric oxide, and some ECM components. Kupffer cells are intrasinusoidally located tissue macrophages with a pronounced endocytic and phagocytic capacity. They are in constant contact with gut-derived particulate materials and soluble bacterial products so that a subthreshold level of their activation in the normal liver may be anticipated. Hepatic macrophages secrete potent mediators of the inflammatory response (reactive oxygen species, eicosanoids, nitric oxide, carbon monoxide, TNF-alpha, and other cytokines), and thus control the early phase of liver inflammation, playing an important part in innate immune defense. High exposure of Kupffer cells to bacterial products, especially endotoxin (lipopolysaccharide, LPS), can lead to the intensive production of inflammatory mediators, and ultimately to liver injury. Besides typical macrophage activities, Kupffer cells play an important role in the clearance of senescent and damaged erythrocytes. Liver macrophages modulate immune responses via antigen presentation, suppression of T-cell activation by antigen-presenting sinusoidal endothelial cells via paracrine actions of IL-10, prostanoids, and TNF-alpha, and participation in the development of oral tolerance to bacterial superantigens. Moreover, during liver injury and inflammation, Kupffer cells secrete enzymes and cytokines that may damage hepatocytes, and are active in the remodeling of extracellular matrix. Hepatic stellate cells are present in the perisinusoidal space. They are characterized by abundance of intracytoplasmic fat droplets and the presence of well-branched cytoplasmic processes, which embrace endothelial cells and provide focally a double lining for sinusoid. In the normal liver HSC store vitamin A, control turnover of extracellular matrix, and regulate the contractility of sinusoids. Acute damage to hepatocytes activates transformation of quiescent stellate cells into myofibroblast-like cells that play a key role in the development of inflammatory fibrotic response. Pit cells represent a liver-associated population of large granular lymphocytes, i.e., natural killer (NK) cells. They spontaneously kill a variety of **tumor** cells in an MHC-unrestricted way, and this antitumor activity may be enhanced by the secretion of interferon-gamma. Besides pit cells, the adult liver contains other subpopulations of lymphocytes such as gamma delta T cells, and both "conventional" and "unconventional" alpha beta T cells, the latter containing liver-specific NK T cells. The development of methods for the isolation and culture of main liver cell types allowed to demonstrate that both nonparenchymal and parenchymal cells secrete tens of mediators that exert multiple paracrine and autocrine actions. Co-culture experiments and analyses of the effects of conditioned media on cultures of another liver cell type have enabled the identification of many substances released from non-parenchymal liver cells that evidently regulate some important functions of neighboring hepatocytes and non-hepatocytes. To the key mediators involved in the intercellular communication in the liver belong prostanoids, nitric oxide, endothelin-1, TNF-alpha, interleukins, and chemokines, many growth factors (TGF-beta, PDGF, IGF-I, HGF), and reactive oxygen species (ROS). Paradoxically, the cooperation of liver cells is better understood under some pathological conditions (i.e., in experimental models of liver injury) than in normal liver due to the possibility of comparing cellular phenotype under in vivo and in vitro conditions with the functions of the injured organ. The

regulation of vitamin A metabolism provides an example of the physiological role for cellular **cross**-talk in the normal liver. The majority (up to 80%) of the total body vitamin A is stored in the liver as long-chain fatty acid **esters** of retinal, serving as the main source of retinoids that are utilized by all tissues throughout the body. Hepatocytes are directly involved in the uptake from blood of chylomicron remnants, and the synthesis of retinol-binding protein that transfers retinol to other tissues. However, more than 80% of the liver retinoids are stored in lipid droplets of hepatic stellate cells. HSC are capable of both uptake and release of retinol depending on the body's retinol status. The activity of some major enzymes of vitamin A metabolism have been found to be many times higher per protein basis in stellate cells than in hepatocytes. Despite progress in the understanding of the roles played by these two cell types in hepatic retinoid metabolism, the way in which retinoids move between the parenchymal cells, stellate cells, and blood plasma has not been fully elucidated. Sinusoidal blood flow is, to a great extent, regulated by hepatic stellate cells that can contract due to the presence of smooth muscle alpha-actin. The main vasoactive substances that affect constriction or relaxation of HSC derive both from distant sources and from neighboring hepatocytes (carbon monoxide, leukotrienes), endothelial cells (endothelin, nitric oxide, prostaglandins), Kupffer cells (prostaglandins, NO), and stellate cells themselves (endothelin, NO). The cellular **cross**-talk reflected by the fine-tuned modulation of sinusoidal contraction becomes disturbed under pathological conditions, such as endotoxemia or liver fibrosis, through the excess synthesis of vasoregulatory compounds and the involvement of additional mediators acting in a paracrine way. The liver is an important source of some growth factors and growth factor-binding proteins. Although hepatocytes synthesize the bulk of insulin-like growth factor I (IGF-I), also other types of nonparenchymal liver cells may produce this peptide. Cell-specific expression of distinct IGF-binding proteins observed in the rat and human liver provides the potential for specific regulation of hepatic IGF-I synthesis not only by growth hormone, insulin, and IGF-I, but also by cytokines released from activated Kupffer (IL-1, TNF-alpha, TGF-beta) or stellate cells (TGF-alpha, TGF-beta). Hepatic stellate cells may affect turnover of hepatocytes through the synthesis of potent positive as well as negative signals such as, respectively, hepatocyte-growth-factor or TGF-beta. Although hepatocytes seem not to produce TGF-beta, a pleiotropic cytokine synthesized and secreted in the latent form by Kupffer and stellate cells, they may contribute to its actions in the liver by the intracellular activation of latent TGF-beta, and secretion of the biologically active isoform. Many mediators that reach the liver during inflammatory processes, such as endotoxins, immune-complexes, anaphylatoxins, and PAF, increase glucose output in the perfused liver, but fail to do so in isolated hepatocytes, acting indirectly via prostaglandins released from Kupffer cells. In the liver, prostaglandins synthesized from arachidonic acid mainly in Kupffer cells in a response to various inflammatory stimuli, modulate hepatic glucose metabolism by increasing glycogenolysis in adjacent hepatocytes. The release of glucose from glycogen supports the increased demand for energetic fuel by the inflammatory cells such as leukocytes, and additionally enables enhanced glucose turnover in sinusoidal endothelial cells and Kupffer cells which is necessary for effective defense of these cells against invading microorganisms and oxidative stress in the liver. Leukotrienes, another oxidation product of arachidonic acid, have vasoconstrictive, cholestatic, and metabolic effects in the liver. A transcellular synthesis of cysteinyl leukotrienes (LTC4, LTD4, and LTE4) functions in the liver: LTA4, an important intermediate, is synthesized in Kupffer cells, taken up by hepatocytes, converted into the potent LTC4, and then released into extracellular space, acting in a paracrine way on Kupffer and sinusoidal endothelial cells. Thus, hepatocytes are target cells for the action of eicosanoids and the site of their transformation and degradation, but can not directly oxidate arachidonic acid to eicosanoids. (ABSTRACT TRUNCATED)

L5 ANSWER 7 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2001389652 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11420253
TITLE: TSG-6 is concentrated in the extracellular matrix of mouse cumulus oocyte complexes through hyaluronan and inter-alpha-inhibitor binding.
AUTHOR: Carrette O; Nemade R V; Day A J; Brickner A; Larsen W J
CORPORATE SOURCE: Department of Cell Biology, Neurobiology and Anatomy, Vontz Center for Molecular Studies, University of Cincinnati, Cincinnati, Ohio 45267-0521, USA.. odile.carrette@uc.edu
CONTRACT NUMBER: HD-29894 (NICHD)
T32 HD-07463-05 (NICHD)
SOURCE: Biology of reproduction, (2001 Jul) Vol. 65, No. 1, pp. 301-8.
Journal code: 0207224. ISSN: 0006-3363.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 8 Oct 2001
Last Updated on STN: 8 Oct 2001
Entered Medline: 4 Oct 2001

AB During development of ovarian follicles in mammals, cumulus cells and the oocyte form a mucoelastic mass that detaches itself from peripheral granulosa cell layers upon an ovulatory surge. The integrity of this cumulus-oocyte complex (COC) relies on the cohesiveness of a **hyaluronan** (HA)-enriched extracellular matrix (ECM). We previously identified a serum glycoprotein, inter-alpha-inhibitor (IalphaI), that is critical in organizing and stabilizing this matrix. Following an ovulatory stimulus, IalphaI diffuses into the follicular fluid and becomes integrated in the ECM through its association with HA. TSG-6 (the secreted product of the **tumor** necrosis factor-stimulated gene 6), another HA binding protein, forms a complex with IalphaI in synovial fluid. The purpose of this study was to investigate whether TSG-6 is involved in the ECM organization of COCs. Immunolocalization of TSG-6 and IalphaI in mouse COCs at different ovulatory stages was analyzed by immunofluorescence and laser confocal microscopy. IalphaI, TSG-6, and HA colocolized in the cumulus ECM. **Western** blot analyses were consistent with the presence of both TSG-6 and TSG-6/IalphaI complexes in ovulated COCs. These results suggest that TSG-6 has a structural role in COC matrix formation possibly mediating **cross**-linking of separate HA molecules through its binding to IalphaI.

L5 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2001326509 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11394655
TITLE: Differential expression of CD44 isoforms during liver regeneration in rats.
AUTHOR: Della Fazia M A; Pettirossi V; Ayroldi E; Riccardi C; Magni M V; Servillo G
CORPORATE SOURCE: Dipartimento di Scienze Biochimiche e di Biotecnologie Molecolari, Universita di Perugia, Policlinico Monteluce, Italy.
SOURCE: Journal of hepatology, (2001 Apr) Vol. 34, No. 4, pp. 555-61.
Journal code: 8503886. ISSN: 0168-8278.
PUB. COUNTRY: Denmark
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110

ENTRY DATE: Entered STN: 15 Oct 2001
Last Updated on STN: 15 Oct 2001
Entered Medline: 11 Oct 2001

AB BACKGROUND: CD44 is a transmembrane glycoprotein known to bind **hyaluronic** acid (HA). This molecule is a multifunctional cell surface glycoprotein involved in lymphocyte homing and activation, **tumor** growth and metastasis. We have investigated the qualitative modification of CD44 in the regenerating liver as a model for studying cellular proliferation in vivo. Molecules involved in cell adhesion and the extracellular matrix (ECM), which influence differentiation, growth, cell-cell interactions and cellular polarity, play an important role in the liver regeneration. We studied the modulation of CD44 gene expression and its post-transcriptional modifications, analyzing the expression of different isoforms containing exon v6 in the regenerating liver, in sham operated liver and in the hepatoma cells H-35. METHODS: The expression of CD44 and CD44v6 were analyzed in RNA extracted from regenerating liver at different times after partial hepatectomy (PH), and H-35 hepatoma cells by Northern blot, RT-PCR and Southern blot, and in protein extracts from regenerating liver by **Western** blot. H-35 hepatoma cells were assayed with the antibody **cross**-linked technique with CD44 antibodies. RESULTS: The standard CD44 form is expressed in regenerating liver and its levels were not modified following PH. However, our analysis revealed CD44 isoforms containing v6 in the first hours after PH as well as in the H-35 hepatoma cell line. H-35 cells treated with **cross**-linked anti-CD44 antibodies or HA show an increased rate of incorporation of [3H]thymidine (30 and 25%, respectively) with respect to the control. CONCLUSION: These findings suggest that CD44 may play a role in the proliferation of residual hepatocytes following PH.

L9 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:380441 CAPLUS
DOCUMENT NUMBER: 125:55014
TITLE: Altered expression of CD44 isoforms in squamous-cell carcinomas and cell lines derived from them
AUTHOR(S): Hudson, David L.; Speight, Paul M.; Watt, Fiona M.
CORPORATE SOURCE: Keratinocyte Laboratory, Imperial Cancer Research Fund, London, WC2A 3PX, UK
SOURCE: International Journal of Cancer (1996), 66(4), 457-463
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss
DOCUMENT TYPE: Journal
LANGUAGE: English

AB CD44 is a transmembrane glycoprotein that binds **hyaluronan**, extracellular matrix proteins and growth factors. Multiple isoforms of CD44 are generated by alternative splicing of 10 sep. exons (V1-V10). Expression of the variable exons has been correlated with **tumor** progression and metastasis in a range of cell types. However, multiple CD44 isoforms are expressed by normal stratified squamous epithelia, such as the epidermis and the lining of the oral **cavity**. The purpose of this study was to examine CD44 expression in squamous-cell carcinomas (SCC). By immunofluorescence the authors found reduced expression of one or more of the variant exons in a series of 13 oral SCC, with loss being most common in poorly differentiated **tumors**. Of the exons examined, V3 was lost most frequently, but otherwise there was no consistent pattern as to which exons (V4/5, 6, 8) were missing. The authors also studied CD44 expression in a range of SCC lines, using **Western** blotting and semi-quant. RT-PCR. All lines showed reduced expression of the terminal differentiation marker involucrin. Two lines showed selective loss of the largest forms of CD44 and one failed to express any of the variant exons. These cell lines, therefore, provide a useful exptl. model with which to study the biol. significance of exon loss in SCC.

L10 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:405314 CAPLUS
TITLE: HYTAD1-p20: A new paclitaxel-hyaluronic acid hydrosoluble bioconjugate for treatment of superficial bladder cancer
AUTHOR(S): Rosato, Antonio; Banzato, Alessandra; De Luca, Gilda; Renier, Davide; Bettella, Fabio; Pagano, Claudio; Esposito, Giovanni; Zanovello, Paola; Bassi, PierFrancesco
CORPORATE SOURCE: Department of Oncology and Surgical Sciences, Oncology Section, University of Padova, Padua, Italy
SOURCE: Urologic Oncology: Seminars and Original Investigations (2006), 24(3), 207-215
CODEN: UOSOAA
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Objective: To report the development of a new water-soluble paclitaxel-**hyaluronic** acid bioconjugate, HYTAD1-p20, for intravesical treatment of superficial bladder cancer. Materials and Methods: HYTAD1-p20 was synthesized by **carboxyl esterification** of **hyaluronic** acid with paclitaxel, and its physicochem. and biol. properties were characterized. Results: Paclitaxel loading was optimized at 20% weight/weight; this procedure increased by 500-fold the paclitaxel concentration in the resulting water-soluble biomaterial. In vitro, HYTAD1-p20 exerted a much higher dose-dependent inhibitory effect against RT-4 and RT-112/84 bladder carcinoma cell growth than that of free drug, and directly interacted with CD44 expressed by bladder **tumor** cells. In vivo, results of pharmacokinetic studies performed in mice after bladder catheterization and intravesical instillation of HYTAD1-p20 disclosed that drug leakage was negligible during a 2-h anal. Histol. examination of drug-instilled bladders revealed that HYTAD1-p20 was extremely well tolerated, while paclitaxel alone produced mucosal disruption and submucosal infiltration of inflammatory cells. Treatment of severe combined immunodeficient mice bearing s.c. RT-112/84 **tumors** with maximum tolerated doses of bioconjugate or paclitaxel showed that HYTAD1-p20 exerted a therapeutic activity comparable to that of free drug. Conclusions: These data suggest that HYTAD1-p20 significantly improved results obtained with conventional paclitaxel in terms of hydrosoly., in vitro activity against human bladder cancer cells, and in vivo biocompatibility. This bioconjugate is a potentially useful treatment for superficial urothelial malignancy.

L10 ANSWER 2 OF 2 MEDLINE on STN
ACCESSION NUMBER: 2006255644 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 16678050
TITLE: HYTAD1-p20: a new paclitaxel-hyaluronic acid hydrosoluble bioconjugate for treatment of superficial bladder cancer.
AUTHOR: Rosato Antonio; Banzato Alessandra; De Luca Gilda; Renier Davide; Bettella Fabio; Pagano Claudio; Esposito Giovanni; Zanovello Paola; Bassi PierFrancesco
CORPORATE SOURCE: Department of Oncology and Surgical Sciences, Oncology Section, University of Padua, Padua, Italy.. antonio.rosato@unipd.it
SOURCE: Urologic oncology, (2006 May-Jun) Vol. 24, No. 3, pp. 207-15.
Journal code: 9805460. ISSN: 1078-1439.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 9 May 2006
Last Updated on STN: 31 May 2006

AB OBJECTIVE: To report the development of a new water-soluble paclitaxel-**hyaluronic** acid bioconjugate, HYTAD1-p20, for intravesical treatment of superficial bladder cancer. MATERIALS AND METHODS: HYTAD1-p20 was synthesized by **carboxyl esterification** of **hyaluronic** acid with paclitaxel, and its physicochemical and biologic properties were characterized. RESULTS: Paclitaxel loading was optimized at 20% w/w; this procedure increased by 500-fold the paclitaxel concentration in the resulting water-soluble biomaterial. In vitro, HYTAD1-p20 exerted a much higher dose-dependent inhibitory effect against RT-4 and RT-112/84 bladder carcinoma cell growth than that of free drug, and directly interacted with CD44 expressed by bladder **tumor** cells. In vivo, results of pharmacokinetic studies performed in mice after bladder catheterization and intravesical instillation of HYTAD1-p20 disclosed that drug leakage was negligible during a 2-hour analysis. Histologic examination of drug-instilled bladders revealed that HYTAD1-p20 was extremely well tolerated, while paclitaxel alone produced mucosal disruption and submucosal infiltration of inflammatory cells. Treatment of severe combined immunodeficient mice bearing subcutaneous RT-112/84 **tumors** with maximum tolerated doses of bioconjugate or paclitaxel showed that HYTAD1-p20 exerted a therapeutic activity comparable to that of free drug. CONCLUSIONS: These data suggest that HYTAD1-p20 significantly improved results obtained with conventional paclitaxel in terms of hydrosolubility, in vitro activity against human bladder cancer cells, and in vivo biocompatibility. This bioconjugate is a potentially useful treatment for superficial urothelial malignancy.

L11 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2006:480565 CAPLUS

TITLE: Lymphatic endothelium-specific hyaluronan receptor LYVE-1 is expressed by stabilin-1+, F4/80+, CD11b+ macrophages in malignant tumours and wound healing tissue in vivo and in bone marrow cultures in vitro: implications for the assessment of lymphangiogenesis

AUTHOR(S): Schledzewski, K.; Falkowski, M.; Moldenhauer, G.; Metharom, P.; Kzhyshkowska, J.; Ganss, R.; Demory, A.; Falkowska-Hansen, B.; Kurzen, H.; Ugurel, S.; Geginat, G.; Arnold, B.; Goerdt, S.

CORPORATE SOURCE: Department of Dermatology, Venerology, and Allergy, University Medical Centre Mannheim, Ruprecht-Karls University Heidelberg, Germany

SOURCE: Journal of Pathology (2006), 209(1), 67-77
CODEN: JPTLAS; ISSN: 0022-3417

PUBLISHER: John Wiley & Sons Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Lymphangiogenesis is a novel prognostic parameter for several cancers that is preferentially quantified by immunohistochem. of the lymphatic endothelium-specific **hyaluronan** receptor LYVE-1. Recently, the specificity of LYVE-1 was challenged by serendipitous observations of LYVE-1 expression in rare tissue macrophages. As expression of the **hyaluronan** receptor-like mol. stabilin-1 is shared by sinusoidal endothelium and macrophages, a thorough anal. of LYVE-1 expression was performed using macrophage-specific markers in vivo and in vitro. In murine **tumor** models and **excisional** wound healing, LYVE-1 expression occurred in a subset of CD11b+, F4/80+ tissue macrophages that preferentially co-expressed stabilin-1. Upon comparison of single- and double-labeling immunofluorescence, it became apparent that LYVE-1+ macrophages mimic sprouting and collapsed lymphatic vessels. In vitro, LYVE-1 expression was induced in 25-40% of murine bone marrow-derived macrophages upon exposure to B16F1 melanoma-conditioned medium and IL-4/dexamethasone. By FACS anal., 11.5% of bone marrow-derived macrophages were LYVE-1+, stabilin-1+ double-pos., while 9.9% were LYVE-1+, stabilin-1- and 33.5% were LYVE-1-, stabilin-1+. Northern and **western** analyses confirmed expression of LYVE-1 mRNA and protein in bone marrow-derived macrophages. In the light of the current debate about true endothelial trans-differentiation vs. endothelial mimicry of monocytes/macrophages, LYVE-1+, stabilin-1+ non-continuous endothelial-like macrophages will require further developmental and functional analyses. In conclusion, the findings imply that LYVE-1 staining must be supplemented by double labeling with macrophage markers in order to differentiate clearly between LYVE-1+ lymphatics and LYVE-1+ **tumor**-infiltrating macrophages. This improved approach will help to clarify the prognostic significance of lymphangiogenesis in malignant **tumors**.

REFERENCE COUNT: 38 THERE ARE 38 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1075830 CAPLUS
DOCUMENT NUMBER: 143:360080
TITLE: Hyaluronic acid butyric esters with a low degree of substitution, procedure for their preparation, and their use in the treatment of cancer
INVENTOR(S): Coradini, Danila; Perbellini, Alberto
PATENT ASSIGNEE(S): Sintofarm S.p.A., Italy; Ferlini, Giovanna
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092929	A1	20051006	WO 2005-IB780	20050325
WO 2005092929	C1	20060302		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 2004-MI605 A 20040329
OTHER SOURCE(S): CASREACT 143:360080
AB The invention discloses **hyaluronic** acid butyric **esters** in which the hydroxyl groups of **hyaluronic** acid are partially **esterified** with butyric residues, characterized by a degree of substitution with butyric residues (ratio of number of butyric acid residues to disaccharide units GIcNAc-GIcUA of **hyaluronic** acid) being equal or below 0.1. These **esters** with low degree of substitution are obtained by means of a process carried out in the homogeneous phase under anhydrous conditions, wherein **hyaluronic** acid is used in the form of a quaternary nitrogen salt. The **esters** of the invention have a greater antiproliferative activity than corresponding **esters** with higher degree of substitution, and are particularly active against primary and metastatic **tumors**, where the **tumors** are primary of hepatic origin, or are hepatic metastases. A further aspect of the invention is represented by pharmaceutical compns., containing as active principle at least one of the **esters** described.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> d L13 1-11 ibib abs

L13 ANSWER 1 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1075830 CAPLUS
DOCUMENT NUMBER: 143:360080
TITLE: Hyaluronic acid butyric esters with a low degree of substitution, procedure for their preparation, and their use in the treatment of cancer
INVENTOR(S): Coradini, Danila; Perbellini, Alberto
PATENT ASSIGNEE(S): Sintofarm S.p.A., Italy; Ferlini, Giovanna
SOURCE: PCT Int. Appl., 37 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092929	A1	20051006	WO 2005-IB780	20050325
WO 2005092929	C1	20060302		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 2004-MI605 A 20040329
OTHER SOURCE(S): CASREACT 143:360080

AB The invention discloses **hyaluronic** acid butyric **esters** in which the hydroxyl groups of **hyaluronic** acid are partially **esterified** with butyric residues, characterized by a degree of substitution with butyric residues (ratio of number of butyric acid residues to disaccharide units GlcNAc-GlcUA of **hyaluronic** acid) being equal or below 0.1. These **esters** with low degree of substitution are obtained by means of a process carried out in the homogeneous phase under anhydrous conditions, wherein **hyaluronic** acid is used in the form of a quaternary nitrogen salt. The **esters** of the invention have a greater antiproliferative activity than corresponding **esters** with higher degree of substitution, and are particularly active against primary and metastatic **tumors**, where the **tumors** are primary of hepatic origin, or are hepatic metastases. A further aspect of the invention is represented by pharmaceutical compns., containing as active principle at least one of the **esters** described.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 2 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:591962 CAPLUS
DOCUMENT NUMBER: 143:91004
TITLE: Use of PSP64 and subfragments to suppress cell adhesion and migration, inhibit matrix metalloproteinase secretion, and treat cancer and other diseases
INVENTOR(S): Panchal, Chandra J.; Wu, Jinzi Jason; Beliveau, Richard; Ruiz, Marcia; Garde, Seema; Annabi, Borhane; Lamy, Sylvie; Bouzeghrane, Mounia; Daigneault, Luc; Hawkins, Robert
PATENT ASSIGNEE(S): Can.
SOURCE: U.S. Pat. Appl. Publ., 59 pp., Cont.-in-part of U.S. Ser. No. 948,229.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 2005147601 A1 20050707 US 2004-4270 20041202
CA 2441695 AA 20050326 CA 2003-2441695 20030926
US 2005096273 A1 20050505 US 2004-948229 20040924
WO 2005118623 A1 20051215 WO 2005-CA430 20050321
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:
CA 2003-2441695 A 20030926
US 2004-948229 A2 20040924
US 2004-857358 A 20040601
US 2004-4270 A 20041202
US 2004-4273 A 20041202

AB Matrix metalloproteinases (MMPs) play an important role in morphogenesis, angiogenesis, wound healing, and in certain disorders such as rheumatoid arthritis, **tumor** invasion and metastasis. MMPs are thought to be regulated by a variety of cytokines, growth factors, hormones and phorbol **esters**. This regulation occurs on three levels; alteration of gene expression, activation of the latent zymogen and inhibition by the tissue inhibitors of metalloproteinases (TIMP). We report here a new agent that regulates the level of MMPs, i.e., prostate secretory protein PSP94. Thus, PCK3145, a pentadecapeptide derived from PSP94, significantly decreased levels of MMP-9 in the blood of patients with metastatic adenocarcinoma of the prostate. A **deriv**. of PCK3145 in which the 3 cysteine SH groups were acetaminomethylated, suppressed secretion of MMP from Mat-LyLu cells. This **derivs**. also decreased U-87 cell adhesion to **hyaluronic** acid as well as U-87 cell migration. Further effects of the PSP94 peptide **deriv** . were increased CD44 cell surface shedding and induction of RhoA protein expression.

L13 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:359113 CAPLUS
DOCUMENT NUMBER: 142:85944
TITLE: Hyaluronic-acid butyric esters as promising antineoplastic agents in human lung carcinoma: A preclinical study
AUTHOR(S): Coradini, Danila; Pellizzaro, Cinzia; Abolafio, Gabriella; Bosco, Marco; Scarlata, Ignazio; Cantoni, Silvia; Stucchi, Luca; Zorzet, Sonia; Turrin, Claudia; Sava, Gianni; Perbellini, Alberto; Daidone, Maria Grazia
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Neth.
SOURCE: Investigational New Drugs (2004), 22(3), 207-217
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New promising compds., derived from the **esterification** of **hyaluronic** acid with butyric acid, were investigated in vitro on a non-small cell lung carcinoma cell line (NCI-H460) and an its metastatic subclone (NCI-H460M). All new compds. exerted a dose-dependent inhibitory effect on both cell lines, which expressed CD44, the sp. surface receptor for **hyaluronic** acid, in a very high percentage of cells (90%). HE1, the most effective of these compds., was 10-fold more effective than

sodium butyrate (NaB) in inhibiting cell proliferation. Similarly to NaB, after 24 h of treatment, HE1 affected the expression of three cell cycle-related proteins (p27kip1, p53 and p21waf1) responsible for growth arrest, indicating that the presence of the **hyaluronic** acid backbone does not interfere with the biol. activity. Intratumoral treatment with HE1 demonstrated a marked efficacy on primary **tumor** growth and on lung metastases formation of the murine Lewis Lung Carcinoma model. Altogether, present findings suggest a possible clin. application of these novel butyric pro-drugs in primary and metastatic lung cancer.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:551368 CAPLUS
DOCUMENT NUMBER: 139:122818
TITLE: Biomaterials based on hyaluronic acid for the anti-angiogenic therapy in the treatment of tumors
INVENTOR(S): Fusenig, Norbert E.; Stark, Hans-Juergen; Willhauck, Michael; Pavesio, Alessandra
PATENT ASSIGNEE(S): Fidia Farmaceutici S.p.A., Italy; Deutsches Krebsforschungszentrum (DKFZ)
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057203	A2	20030717	WO 2003-EP78	20030107
WO 2003057203	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2472880	AA	20030717	CA 2003-2472880	20030107
AU 2003201618	A1	20030724	AU 2003-201618	20030107
EP 1463541	A2	20041006	EP 2003-700315	20030107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005524619	T2	20050818	JP 2003-557561	20030107
US 2005037049	A1	20050217	US 2004-501030	20040812

PRIORITY APPLN. INFO.: IT 2002-PD3 A 20020111
WO 2003-EP78 W 20030107

AB The use in the medical-surgical field of biomaterials based on hyaluronic acid **derivs**., optionally in association with natural, synthetic or semi-synthetic biopolymers, for suppressing the angiogenic process associated with tumor proliferation (in primary and secondary tumors) is disclosed. For example, the Hyaff 11-based biomaterial proved able to modulate/inhibit the angiogenic process related to vascularization of the cancerous epithelium.

L13 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1999:246222 CAPLUS
DOCUMENT NUMBER: 131:110966
TITLE: Hyaluronic acid as drug delivery for sodium butyrate: improvement of the anti-proliferative activity on a

breast-cancer cell line
AUTHOR(S): Coradini, Danila; Pellizzaro, Cinzia; Miglierini, Giuliana; Daidone, Maria Grazia; Perbellini, Alberto
CORPORATE SOURCE: Oncologia Sperimentale C, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, 20133, Italy
SOURCE: International Journal of Cancer (1999), 81(3), 411-416
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The potential clin. utility of sodium butyrate, a natural compound known to inhibit **tumor**-cell growth, is hampered by the difficulty of achieving effective in-vivo concns. The short half-life (about 5 min) of sodium butyrate results in rapid metabolism and excretion. To increase the availability of sodium butyrate over a longer period of time, we co-valently linked it to **hyaluronic** acid (a component of the extracellular matrix). Its major advantages as a drug carrier consist in its high biocompatibility and its ability to bind CD44, a specific membrane receptor frequently over-expressed on the **tumor**-cell surface. The degree of substitution of **hyaluronic** acid with butyrate residues ranged from d.s. = 0.10 to d.s. = 2.24 (1.8-28.4% weight/weight). The biol. activity of **hyaluronic**-acid-butyric-**ester derivs**. was evaluated in terms of the inhibition of the growth of the MCF7 cell line and compared with that of sodium butyrate. After 6 days of treatment, we observed a progressive improvement of the anti-proliferative activity up to d.s. = 0.20; thereafter, the anti-proliferative effect of the **ester derivs**. decreased. Fluorescence microscopy showed that after 2 h of treatment fluorescein-labeled compds. appeared to be almost completely internalized into MCF7 cells, expressing CD44 standard and variant isoforms. These findings indicate that **hyaluronic** acid could offer an important advantage in drug delivery, in addition to its biocompatibility: the ability to bind to CD44, which are known to be frequently over-expressed on the **tumor**-cell surface.

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 6 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1996:359752 CAPLUS
DOCUMENT NUMBER: 125:26304
TITLE: Hyaluronic acid and **derivatives** for modulation of cellular activity
INVENTOR(S): Asculai, Samuel Simon
PATENT ASSIGNEE(S): Hyal Pharmaceutical Corporation, Can.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 24
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9606622	A1	19960307	WO 1995-CA477	19950811
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2131130	AA	19960301	CA 1994-2131130	19940830
CA 2145605	AA	19960928	CA 1995-2145605	19950327
AU 9531595	A1	19960322	AU 1995-31595	19950811

EP 778776	A1	19970618	EP 1995-927605		19950811
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE					
HU 76846	A2	19971229	HU 1997-1507		19950811
JP 10504828	T2	19980512	JP 1996-508371		19950811
ZA 9507223	A	19960401	ZA 1995-7223		19950829
CN 1130532	A	19960911	CN 1995-116995		19950829
CA 2268476	AA	19980430	CA 1996-2268476		19961018
AU 9672721	A1	19980515	AU 1996-72721		19961018
AU 739701	B2	20011018			
EP 952855	A1	19991103	EP 1996-934250		19961018
EP 952855	B1	20050727			
R: DE, FR, GB, IT, SE					
NZ 335259	A	20001222	NZ 1996-335259		19961018
ZA 9608847	A	19970527	ZA 1996-8847		19961022
US 6475795	B1	20021105	US 1997-860696		19970616
US 2003036525	A1	20030220	US 2002-234355		20020904
PRIORITY APPLN. INFO.:			CA 1994-2131130	A	19940830
			CA 1995-2145605	A	19950327
			US 1995-468328	A2	19950606
			WO 1995-CA477	W	19950811
			WO 1996-CA700	A	19961018
			US 1997-860696	A1	19970616

AB A method is provided for the modulation of cellular activity of tissue and cells expressing a high affinity cell-surface receptor for the **hyaluronic** acid, e.g. an adhesion mol. (e.g., ICAM-1, HARLEC, CD44) and a regulatory mol. (e.g., RHAMM) of a human. The method comprises the administration of a non-toxic effective amount of a form of **hyaluronic** acid [e.g., **hyaluronic** acid, a salt thereof, (e.g., sodium **hyaluronate** having a mol. weight of less than 750,000 daltons, (e.g., 225,000 daltons)), e.g. from Hyal Pharmaceutical Corp. within the range of 150,000-225,000 daltons and those disclosed in U. S. Patent Application 08/143,983, mol. weight fractions of a form of sodium **hyaluronate** (e.g., fractions disclosed in Canadian Letters Patent 1205031 (to Fidia)) such as those from 50,000-100,000 daltons, 250,000-350,000 daltons, and 500,000-730,000 daltons, or other fractions, homologues, analogs, **derivs**., complexes, **esters**, fragments, and/or subunits of **hyaluronic** acid and/or combinations thereof] and/or **hyaluronic** acid-mimicking mols. to a human to modulate cellular activity of tissues and/or cells expressing a high affinity cell-surface receptor for **hyaluronic** acid, e.g., an adhesion mol. and a regulatory mol. in the human body, in a pharmaceutical excipient tolerable by the human (e.g., sterile water). Dosage amts. of pharmaceutical compns. are also disclosed. The methodol. of the invention is useful for the treatment of e.g. cold, stroke, inflammatory process, fibrosis, or cancer. Studies were performed to determine if accessible **hyaluronic** acid binding sites are present in **tumor** tissue in vivo, and the relation of these possible sites to previously described **hyaluronic** acid-binding proteins. Also, further evidence is presented that HARLEC/ICAM-1 is a receptor for **hyaluronic** acid, that **hyaluronic** acid also targets human **tumors** in nude rats, and that the targeting is mainly via binding to HARLEC/ICAM-1 on **tumor** endothelium.

L13 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER:	1993:574227 CAPLUS
DOCUMENT NUMBER:	119:174227
TITLE:	Hyaluronic acids for treatment of ischemia damage in tissues
INVENTOR(S):	Falk, Rudolf E.; Asculai, Samuel S.; Klein, Ehud S.
PATENT ASSIGNEE(S):	Norpharmco Inc., Can.
SOURCE:	Eur. Pat. Appl., 19 pp. CODEN: EPXXDW
DOCUMENT TYPE:	Patent
LANGUAGE:	English

FAMILY ACC. NUM. COUNT: 24
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 557118	A1	19930825	EP 1993-301230	19930219
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CA 2061567	AA	19930821	CA 1992-2061567	19920220
CA 2061567	C	19980203		
CA 2268476	AA	19980430	CA 1996-2268476	19961018
AU 9672721	A1	19980515	AU 1996-72721	19961018
AU 739701	B2	20011018		
EP 952855	A1	19991103	EP 1996-934250	19961018
EP 952855	B1	20050727		
R: DE, FR, GB, IT, SE				
NZ 335259	A	20001222	NZ 1996-335259	19961018
ZA 9608847	A	19970527	ZA 1996-8847	19961022
US 6475795	B1	20021105	US 1997-860696	19970616
US 2003036525	A1	20030220	US 2002-234355	20020904
PRIORITY APPLN. INFO.:			CA 1992-2061567 A	19920220
			WO 1996-CA700 A	19961018
			US 1997-860696 A1	19970616

AB **Hyaluronic** acid (I), salts, homologs, analogs, **derivs**., complexes, **esters**, fragments, and units thereof are used for treatment of ischemia damage in tissues. Rats with liver-implanted mammary carcinoma were given i.v. injection of 3H 5-fluorouracil (II) and I. The uptake of II by **tumor** tissues was 40% more in I-treated animals than untreated ones.

L13 ANSWER 8 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2005115084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15746573
TITLE: Hyaluronic acid butyric esters in cancer therapy.
AUTHOR: Speranza Annalisa; Pellizzaro Cinzia; Coradini Danila
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
SOURCE: Anti-cancer drugs, (2005 Apr) Vol. 16, No. 4, pp. 373-9.
Ref: 32
Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200507
ENTRY DATE: Entered STN: 5 Mar 2005
Last Updated on STN: 6 Jul 2005
Entered Medline: 5 Jul 2005

AB In this review we focus on a promising novel histone deacetylase (HDAC) inhibitor (HA-But) obtained by the **esterification** of butyric acid (BA), the smallest HDAC inhibitor, with **hyaluronic** acid (HA), the main constituent of the extracellular matrix which selectively recognizes a transmembrane receptor (CD44) overexpressed in most primary cancers and associated with **tumor** progression. In vitro, HA-But has proved to be 10-fold more effective than BA in inhibiting the proliferation of a panel of human cancer cell lines, representative of the most common human cancers, and, similar to BA, to regulate the expression of some cell cycle-related proteins, to induce growth arrest in the G1/G0 phase of the cell cycle and to increase histone acetylation. In vivo, HA-But treatment has demonstrated a marked potency in inhibiting primary **tumor** growth and lung metastases formation from murine Lewis lung carcinoma (LL3) as well as liver metastases formation from intrasplenic implantation of LL3 or B16-F10 murine melanoma cells. In particular, the

effect of s.c. and i.p. treatment with HA-But on liver metastases resulted, respectively, in 87 and 100% metastases-free animals, and in a significant prolongation of the survival time compared to the control groups. The results suggest that the presence of the HA backbone does not interfere with the biological activity of butyric residues and that HA-But could represent a promising cell-targetable antineoplastic agent for the treatment of primary and metastatic **tumors**.

L13 ANSWER 9 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2004305776 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15090545
TITLE: CD44 interaction with Na+-H+ exchanger (NHE1) creates acidic microenvironments leading to hyaluronidase-2 and cathepsin B activation and breast tumor cell invasion.
AUTHOR: Bourguignon Lilly Y W; Singleton Patrick A; Diedrich Falko; Stern Robert; Gilad Eli
CORPORATE SOURCE: Department of Medicine, University of California, Veterans Affairs Medical Center, San Francisco 94121, USA.. lillyb@itsa.ucsf.edu
CONTRACT NUMBER: P01 AR39448 (NIAMS)
R01 CA66163 (NCI)
R01 CA78633 (NCI)
SOURCE: The Journal of biological chemistry, (2004 Jun 25) Vol. 279, No. 26, pp. 26991-7007. Electronic Publication: 2004-04-16.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 24 Jun 2004
Last Updated on STN: 14 Aug 2004
Entered Medline: 13 Aug 2004

AB We have explored CD44 (a **hyaluronan** (HA) receptor) interaction with a Na(+)-H(+) exchanger (NHE1) and **hyaluronidase**-2 (Hyal-2) during HA-induced cellular signaling in human breast **tumor** cells (MDA-MB-231 cell line). Immunological analyses demonstrate that CD44s (standard form) and two signaling molecules (NHE1 and Hyal-2) are closely associated in a complex in MDA-MB-231 cells. These three proteins are also significantly enriched in **cholesterol** and ganglioside-containing lipid rafts, characterized as caveolin and flotillin-rich plasma membrane microdomains. The binding of HA to CD44 activates Na(+)-H(+) exchange activity which, in turn, promotes intracellular acidification and creates an acidic extracellular matrix environment. This leads to Hyal-2-mediated HA catabolism, HA modification, and cysteine proteinase (cathepsin B) activation resulting in breast **tumor** cell invasion. In addition, we have observed the following: (i) HA/CD44-activated Rho kinase (ROK) mediates NHE1 phosphorylation and activity, and (ii) inhibition of ROK or NHE1 activity (by treating cells with a ROK inhibitor, Y27632, or NHE1 blocker, S-(N-ethyl-N-isopropyl) amiloride, respectively) blocks NHE1 phosphorylation/Na(+)-H(+) exchange activity, reduces intracellular acidification, eliminates the acidic environment in the extracellular matrix, and suppresses breast **tumor**-specific behaviors (e.g. Hyal-2-mediated HA modification, cathepsin B activation, and **tumor** cell invasion). Finally, down-regulation of CD44 or Hyal-2 expression (by treating cells with CD44 or Hyal-2-specific small interfering RNAs) not only inhibits HA-mediated CD44 signaling (e.g. ROK-mediated Na(+)-H(+) exchanger reaction and cellular pH changes) but also impairs oncogenic events (e.g. Hyal-2 activity, **hyaluronan** modification, cathepsin B activation, and **tumor** cell invasion). Taken together, our results suggest that CD44 interaction with a ROK-activated NHE1 (a Na(+)-H(+) exchanger) in **cholesterol**/ganglioside-

containing lipid rafts plays a pivotal role in promoting intracellular/extracellular acidification required for Hyal-2 and cysteine proteinase-mediated matrix degradation and breast cancer progression.

L13 ANSWER 10 OF 11 MEDLINE on STN
ACCESSION NUMBER: 2004222806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15122068
TITLE: Hyaluronic-acid butyric esters as promising antineoplastic agents in human lung carcinoma: a preclinical study.
AUTHOR: Coradini Danila; Pellizzaro Cinzia; Abolafio Gabriella; Bosco Marco; Scarlata Ignazio; Cantoni Silvia; Stucchi Luca; Zorzet Sonia; Turrin Claudia; Sava Gianni; Perbellini Alberto; Daidone Maria Grazia
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy.. danila.coradini@istitutotumori.mi.it
SOURCE: Investigational new drugs, (2004 Aug) Vol. 22, No. 3, pp. 207-17.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 5 May 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 22 Nov 2004

AB New promising compounds, derived from the **esterification** of **hyaluronic** acid with butyric acid, were investigated in vitro on a non-small cell lung carcinoma cell line (NCI-H460) and an its metastatic subclone (NCI-H460M). All new compounds exerted a dose-dependent inhibitory effect on both cell lines, which expressed CD44, the specific surface receptor for **hyaluronic** acid, in a very high percentage of cells (90%). HE1, the most effective of these compounds, was 10-fold more effective than sodium butyrate (NaB) in inhibiting cell proliferation. Similarly to NaB, after 24 hours of treatment, HE1 affected the expression of three cell cycle-related proteins (p27(kip1), p53 and p21(waf1)) responsible for growth arrest, indicating that the presence of the **hyaluronic** acid backbone does not interfere with the biologic activity. Intratumoral treatment with HE1 demonstrated a marked efficacy on primary **tumor** growth and on lung metastases formation of the murine Lewis Lung Carcinoma model. Altogether, present findings suggest a possible clinical application of these novel butyric pro-drugs in primary and metastatic lung cancer.

L13 ANSWER 11 OF 11 MEDLINE on STN
ACCESSION NUMBER: 1999224662 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10209956
TITLE: Hyaluronic acid as drug delivery for sodium butyrate: improvement of the anti-proliferative activity on a breast-cancer cell line.
AUTHOR: Coradini D; Pellizzaro C; Miglierini G; Daidone M G; Perbellini A
CORPORATE SOURCE: Oncologia Sperimentale C, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.. coradini@istitutotumori.mi.it
SOURCE: International journal of cancer. Journal international du cancer, (1999 May 5) Vol. 81, No. 3, pp. 411-6.
Journal code: 0042124. ISSN: 0020-7136.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 11 May 1999
Last Updated on STN: 11 May 1999
Entered Medline: 29 Apr 1999

AB The potential clinical utility of sodium butyrate, a natural compound known to inhibit **tumor**-cell growth, is hampered by the difficulty of achieving effective in-vivo concentrations. The short half-life (about 5 minutes) of sodium butyrate results in rapid metabolism and excretion. To increase the availability of sodium butyrate over a longer period of time, we co-valently linked it to **hyaluronic** acid (a component of the extracellular matrix). Its major advantages as a drug carrier consist in its high biocompatibility and its ability to bind CD44, a specific membrane receptor frequently over-expressed on the **tumor**-cell surface. The degree of substitution of **hyaluronic** acid with butyrate residues ranged from d.s.=0.10 to d.s.=2.24 (1.8-28.4% w/w). The biological activity of **hyaluronic** -acid-butyric-**ester derivatives** was evaluated in terms of the inhibition of the growth of the MCF7 cell line and compared with that of sodium butyrate. After 6 days of treatment, we observed a progressive improvement of the anti-proliferative activity up to d.s.=0.20; thereafter, the anti-proliferative effect of the **ester derivatives** decreased. Fluorescence microscopy showed that after 2 hr of treatment fluorescein-labelled compounds appeared to be almost completely internalized into MCF7 cells, expressing CD44 standard and variant isoforms. These findings indicate that **hyaluronic** acid could offer an important advantage in drug delivery, in addition to its biocompatibility: the ability to bind to CD44, which are known to be frequently over-expressed on the **tumor**-cell surface.

L17 ANSWER 1 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:474022 CAPLUS
TITLE: Translational event mediates differential production of tumor necrosis factor-α in hyaluronan-stimulated microglia and macrophages
AUTHOR(S): Wang, Mei-Jen; Kuo, Jon-Son; Lee, Wen-Wen; Huang, Hsin-Yi; Chen, Wu-Fu; Lin, Shinn-Zong
CORPORATE SOURCE: Neuro-Medical Scientific Center, Tzu-Chi College of Technology, Buddhist Tzu-Chi General Hospital, Hualien, Taiwan
SOURCE: Journal of Neurochemistry (2006), 97(3), 857-871
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recent evidence has demonstrated that **hyaluronan** synthase 2 mRNA is up-regulated after brain ischemia. After a cerebral ischemic event, microglia and macrophages are the major inflammatory cells and are activated by **hyaluronan** (HA). However, it is unclear how these cells compare with regard to HA responsiveness. The authors show here that peritoneal macrophages and RAW 264.7 macrophages produced more than five- and 10-fold more **tumor** necrosis factor-α (TNF-α) than **primary** microglia and BV-2 microglia, resp. Antibody blockade study showed that CD44, Toll-like receptor-4 receptor and the receptor for HA-mediated motility were responsible for HA-induced TNF-α release. Furthermore, HA induced higher levels of phosphorylated MAPK in RAW 264.7 cells when compared with BV-2 cells. HA-mediated TNF-α production required p38 MAPK, extracellular-regulated kinase and c-Jun N-terminal kinase phosphorylation in both cell types. The levels of HA-induced TNF-α mRNA expression in BV-2 cells were only twofold lower compared with RAW 264.7 cells, suggesting that a translational event is involved in the differential production of TNF-α. **Western** blot anal. revealed that HA treatment resulted in more rapid phosphorylation of eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and more effective dissociation of 4E-BP1 from eukaryotic initiation factor 4E in RAW 264.7 cells than in BV-2 cells. Addnl., HA-induced phosphorylation of 4E-BP1 was dependent on MAPK signaling, indicating that RAW 264.7 cells exhibited higher levels of hyperphosphorylated 4E-BP1 possibly due to the overactivation of MAPK. The results suggest that resident microglia and blood-derived monocytes/macrophages exhibit differential sensitivities in response to extracellular mediators after brain ischemia.
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 2 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1075830 CAPLUS
DOCUMENT NUMBER: 143:360080
TITLE: Hyaluronic acid butyric esters with a low degree of substitution, procedure for their preparation, and their use in the treatment of cancer
INVENTOR(S): Coradini, Danila; Perbellini, Alberto
PATENT ASSIGNEE(S): Sintofarm S.p.A., Italy; Ferlini, Giovanna
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005092929	A1	20051006	WO 2005-IB780	20050325

WO 2005092929 C1 20060302
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: IT 2004-MI605 A 20040329
OTHER SOURCE(S): CASREACT 143:360080

AB The invention discloses **hyaluronic** acid butyric **esters** in which the hydroxyl groups of **hyaluronic** acid are partially **esterified** with butyric residues, characterized by a degree of substitution with butyric residues (ratio of number of butyric acid residues to disaccharide units GIcNAc-GIcUA of **hyaluronic** acid) being equal or below 0.1. These **esters** with low degree of substitution are obtained by means of a process carried out in the homogeneous phase under anhydrous conditions, wherein **hyaluronic** acid is used in the form of a quaternary nitrogen salt. The **esters** of the invention have a greater antiproliferative activity than corresponding **esters** with higher degree of substitution, and are particularly active against **primary** and metastatic **tumors**, where the **tumors** are **primary** of hepatic origin, or are hepatic metastases. A further aspect of the invention is represented by pharmaceutical compns., containing as active principle at least one of the **esters** described.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 3 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:178896 CAPLUS
DOCUMENT NUMBER: 142:384899
TITLE: Hyaluronic acid butyric esters in cancer therapy
AUTHOR(S): Speranza, Annalisa; Pellizzaro, Cinzia; Coradini, Danila
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy
SOURCE: Anti-Cancer Drugs (2005), 16(4), 373-379
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB In this review the authors focus on a promising novel histone deacetylase (HDAC) inhibitor (HA-But) obtained by the **esterification** of butyric acid (BA), the smallest HDAC inhibitor, with **hyaluronic** acid (HA), the main constituent of the extracellular matrix which selectively recognizes a transmembrane receptor (CD44) overexpressed in most **primary** cancers and associated with **tumor** progression. In vitro, HA-But has proved to be 10-fold more effective than BA in inhibiting the proliferation of a panel of human cancer cell lines, representative of the most common human cancers, and, similar to BA, to regulate the expression of some cell cycle-related proteins, to induce growth arrest in the G1/G0 phase of the cell cycle and to increase histone acetylation. In vivo, HA-But treatment has demonstrated a marked potency in inhibiting **primary tumor** growth and lung metastases formation from murine Lewis lung carcinoma (LL3) as well as liver metastases formation from intrasplenic implantation of LL3 or B16-F10 murine melanoma cells. In particular, the effect of s.c. and i.p. treatment with HA-But on liver metastases resulted, resp., in 87 and 100%

metastases-free animals, and in a significant prolongation of the survival time compared to the control groups. The results suggest that the presence of the HA backbone does not interfere with the biol. activity of butyric residues and that HA-But could represent a promising cell-targetable antineoplastic agent for the treatment of **primary** and metastatic **tumors**.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 4 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2004:359113 CAPLUS
DOCUMENT NUMBER: 142:85944
TITLE: Hyaluronic-acid butyric esters as promising antineoplastic agents in human lung carcinoma: A preclinical study
AUTHOR(S): Coradini, Danila; Pellizzaro, Cinzia; Abolafio, Gabriella; Bosco, Marco; Scarlata, Ignazio; Cantoni, Silvia; Stucchi, Luca; Zorzet, Sonia; Turrin, Claudia; Sava, Gianni; Perbellini, Alberto; Daidone, Maria Grazia
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Neth.
SOURCE: Investigational New Drugs (2004), 22(3), 207-217
CODEN: INNDDK; ISSN: 0167-6997
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB New promising compds., derived from the **esterification** of **hyaluronic** acid with butyric acid, were investigated in vitro on a non-small cell lung carcinoma cell line (NCI-H460) and an its metastatic subclone (NCI-H460M). All new compds. exerted a dose-dependent inhibitory effect on both cell lines, which expressed CD44, the sp. surface receptor for **hyaluronic** acid, in a very high percentage of cells (90%). HE1, the most effective of these compds., was 10-fold more effective than sodium butyrate (NaB) in inhibiting cell proliferation. Similarly to NaB, after 24 h of treatment, HE1 affected the expression of three cell cycle-related proteins (p27kip1, p53 and p21waf1) responsible for growth arrest, indicating that the presence of the **hyaluronic** acid backbone does not interfere with the biol. activity. Intratumoral treatment with HE1 demonstrated a marked efficacy on **primary** **tumor** growth and on lung metastases formation of the murine Lewis Lung Carcinoma model. Altogether, present findings suggest a possible clin. application of these novel butyric pro-drugs in **primary** and metastatic lung cancer.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 5 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2003:551368 CAPLUS
DOCUMENT NUMBER: 139:122818
TITLE: Biomaterials based on hyaluronic acid for the anti-angiogenic therapy in the treatment of tumors
INVENTOR(S): Fusenig, Norbert E.; Stark, Hans-Juergen; Willhauck, Michael; Pavesio, Alessandra
PATENT ASSIGNEE(S): Fidia Farmaceutici S.p.A., Italy; Deutsches Krebsforschungszentrum (DKFZ)
SOURCE: PCT Int. Appl., 16 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003057203	A2	20030717	WO 2003-EP78	20030107
WO 2003057203	A3	20031231		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
CA 2472880	AA	20030717	CA 2003-2472880	20030107
AU 2003201618	A1	20030724	AU 2003-201618	20030107
EP 1463541	A2	20041006	EP 2003-700315	20030107
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2005524619	T2	20050818	JP 2003-557561	20030107
US 2005037049	A1	20050217	US 2004-501030	20040812
PRIORITY APPLN. INFO.:			IT 2002-PD3 A	20020111
			WO 2003-EP78 W	20030107

AB The use in the medical-surgical field of biomaterials based on hyaluronic acid derivs., optionally in association with natural, synthetic or semi-synthetic biopolymers, for suppressing the angiogenic process associated with tumor proliferation (in **primary** and secondary tumors) is disclosed. For example, the Hyaff 11-based biomaterial proved able to modulate/inhibit the angiogenic process related to vascularization of the cancerous epithelium.

L17 ANSWER 6 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2002:684914 CAPLUS
DOCUMENT NUMBER: 138:54321
TITLE: Receptor for hyaluronan acid-mediated motility (RHAMM) is a new immunogenic leukemia-associated antigen in acute and chronic myeloid leukemia
AUTHOR(S): Greiner, Jochen; Ringhoffer, Mark; Taniguchi, Masanori; Schmitt, Anita; Kirchner, Dieter; Krahn, Gertraud; Heilmann, Volker; Gschwend, Jurgen; Bergmann, Lothar; Dohner, Hartmut; Schmitt, Michael
CORPORATE SOURCE: Third Department of Internal Medicine and Department of Transfusion Med., University of Ulm, Ulm, Germany
SOURCE: Experimental Hematology (New York, NY, United States) (2002), 30(9), 1029-1035
CODEN: EXHMA6; ISSN: 0301-472X
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Objective. Identification of leukemia-associated antigens (LAA) eliciting an immune response in patients is a prerequisite for specific immunotherapy of leukemias. To identify new LAA, the authors used the method of serol. screening of cDNA expression libraries (SEREX). Materials and Methods. A SEREX library of the cell line K562 was subjected to allogeneic screening with sera from patients with acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) vs sera from healthy volunteers. Results. The receptor for **hyaluronan** acid-mediated motility (RHAMM) involved in cell growth and metastasis was identified as a new LAA. Serol. responses to RHAMM were observed in patients with AML (42%), CML (31%), melanoma (83%), renal cell carcinoma (40%), breast cancer (67%), and ovarian carcinoma (50%), but not in HV or patients with autoimmune diseases. RHAMM mRNA was detectable in peripheral blood mononuclear cells (PBMN) of 60% of newly diagnosed AML patients. **Western** blotting stained pos. for RHAMM protein in 70% of AML patients. mRNA expression of

RHAMM also was found in patients with CML (40%), renal cell carcinoma (73%), breast carcinoma (60%), and ovarian carcinoma (50%). In melanoma, RHAMM mRNA expression was detected in metastases (80%) but not in **primary tumors**. RHAMM is differentially expressed: significant mRNA expression was not found in normal tissues, except from testis, placenta, and thymus, or in PBMN- and CD34-separated cell samples of healthy volunteers. Conclusions. RHAMM is an immunogenic antigen in leukemias and solid **tumors** and might be a potential target structure for cellular immunotherapies and antibody therapies.

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 7 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 2000:352460 CAPLUS

DOCUMENT NUMBER: 133:103634

TITLE: Hyaluronan anchoring and regulation on the surface of vascular endothelial cells is mediated through the functionally active form of CD44

AUTHOR(S): Nandi, Animesh; Estess, Pila; Siegelman, Mark H.

CORPORATE SOURCE: Laboratory of Molecular Pathology, Department of Pathology, The University of Texas Southwestern Medical Center, Dallas, TX, 75235-9072, USA

SOURCE: Journal of Biological Chemistry (2000), 275(20), 14939-14948
CODEN: JBCHA3; ISSN: 0021-9258

PUBLISHER: American Society for Biochemistry and Molecular Biology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB CD44 on lymphocytes binding to its carbohydrate ligand **hyaluronan** can mediate **primary** adhesion (rolling interactions) of lymphocytes on vascular endothelial cells. This adhesion pathway is utilized in the extravasation of activated T cells from the blood into sites of inflammation and therefore influences patterns of lymphocyte homing and inflammation. **Hyaluronan** is a glycosaminoglycan found in the extracellular matrix and is involved in a number of biol. processes. We have shown that the expression of **hyaluronan** on the surface of endothelial cells is inducible by proinflammatory cytokines. However, the manner through which **hyaluronan** is anchored to the endothelial cell surface so that it can resist shear forces and the mechanism of the regulation of the level of **hyaluronan** on the cell surface has not been investigated. In order to characterize potential **hyaluronan** receptors on endothelial cells, we performed analyses of cell surface staining by flow cytometry on intact endothelial cells and ligand blotting assays using membrane fractions. **Hyaluronan** binding activity was detected as a major species corresponding to the size of CD44, and this was confirmed to be the same by **Western** blotting and immunopptn. Moreover, alterations in the surface level of **hyaluronan** after **tumor** necrosis factor-α stimulation is regulated **primarily** by changes in the cell surface levels of the **hyaluronan**-binding form of CD44. In laminar flow assays, lymphoid cells specifically roll on **hyaluronan** anchored by purified CD44 coated on glass tubes, indicating that the avidity of the endothelial CD44/**hyaluronan** interaction is sufficient to support rolling adhesions under conditions mimicking physiol. shear forces. These studies show that CD44 serves to anchor **hyaluronan** on endothelial cell surfaces, that activation of CD44 is a major regulator of endothelial surface **hyaluronan** expression, and that the non-covalent interaction between CD44 and **hyaluronan** is sufficient to provide resistance to shear under physiol. conditions and thereby support the initial steps of lymphocyte extravasation.

REFERENCE COUNT: 87 THERE ARE 87 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 8 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2000:208653 CAPLUS
DOCUMENT NUMBER: 132:346542
TITLE: Heparan sulfate proteoglycan isoforms of the CD44 hyaluronan receptor induced in human inflammatory macrophages can function as paracrine regulators of fibroblast growth factor action
AUTHOR(S): Jones, Margaret; Tussey, Lynda; Athanasou, Nick; Jackson, David G.
CORPORATE SOURCE: Department of Cellular Science, John Radcliffe Hospital, Oxford, OX3 9DU, UK
SOURCE: Journal of Biological Chemistry (2000), 275(11), 7964-7974
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The CD44 glycoprotein is expressed in multiple isoforms on a variety of cell types where it functions as a receptor for **hyaluronan** -mediated motility. Recently, interest has centered on CD44 heparan sulfate proteoglycan (HSPG) isoforms because of their potential to **sequester** heparin-binding growth factors and chemokines. Expression of these isoforms on ectodermal cells has recently been shown to regulate limb morphogenesis via presentation of fibroblast growth factor (FGF) 4/FGF 8 while expression on **tumor** cells was shown to **sequester** hepatocyte growth factor and promote **tumor** dissemination. To date, however, CD44 HSPG expression in tissue macrophages and lymphocytes has not been adequately investigated, despite the fact these cells actively synthesize growth factors and chemokines and indirect evidence that monocyte CD44 **sequesters** macrophage inflammatory protein-1β. Here the authors show **primary** human monocytes rather than lymphocytes express CD44 HSPGs, but only following in vitro differentiation to macrophages or activation with the proinflammatory cytokine interleukin-1α or bacterial lipopolysaccharide. Furthermore, the authors show these isoforms are preferentially modified with heparan rather than chondroitin sulfate, bind the macrophage-derived growth factors FGF-2, vascular endothelial growth factor, and heparin-binding epidermal growth factor with varying affinities (Kd 25-330 nM) and in the case of FGF-2, can stimulate productive binding to the high affinity tyrosine kinase FGF receptor 1 (FGFR1). In contrast, the authors find no evidence for binding to C-C chemokines. Last, the authors confirm by immunofluorescent antibody staining that inflamed synovial membrane macrophages express CD44 HSPGs and that expression is greatest in cells containing high FGF-2 levels. These results suggest a paracrine role for macrophage CD44 HSPG isoforms in the regulation of growth factor action during inflammation.
REFERENCE COUNT: 57 THERE ARE 57 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 9 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 1998:452455 CAPLUS
DOCUMENT NUMBER: 129:201417
TITLE: The human hyaluronan receptor RHAMM is expressed as an intracellular protein in breast cancer cells
AUTHOR(S): Assmann, Volker; Marshall, John F.; Fieber, Christina; Hofmann, Martin; Hart, Ian R.
CORPORATE SOURCE: Richard Dimbleby Department of Cancer Research/ICRF Laboratory, St Thomas' Hospital, London, SE1 7EH, UK
SOURCE: Journal of Cell Science (1998), 111(12), 1685-1694
CODEN: JNCSAI; ISSN: 0021-9533
PUBLISHER: Company of Biologists Ltd.
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The receptor for **hyaluronan** mediated motility (RHAMM) has been reported to mediate migration, transformation, and metastatic spread of murine fibroblasts. Here the authors describe the expression of two human RHAMM isoforms, which are generated by alternative splicing of the **primary** gene transcript, by a series of human breast carcinoma cell lines. A polyclonal antibody, raised against a bacterially expressed RHAMM fusion protein, detected an 85-90 kDa protein by **western** blot anal. No correlation between the level of RHAMM mRNA and protein expression with known metastatic/malignant potential of the **tumor** cell lines was observed Interestingly, the authors found that the antibody did not stain the cell surface but the cytoplasm of breast cancer cells. The intracellular localization of RHAMM was confirmed by subcellular fractionation studies. RHAMM proteins were capable of binding to **hyaluronan**, but not to heparin or chondroitin sulfate, in an vitro binding assay. The authors also provide evidence that a potential **hyaluronan**-binding motif in the N-terminus of the protein is not involved in the interaction of RHAMM with **hyaluronan**. The findings lead the authors' to conclude that RHAMM does not function as a conventional motility receptor for HA in human breast cancer cells and the authors suggest the term RHAMM be substituted by "intracellular **hyaluronic** acid binding protein" (IHABP).

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L17 ANSWER 10 OF 20 CAPLUS COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 1990:30845 CAPLUS

DOCUMENT NUMBER: 112:30845

TITLE: Effects of thyroid-stimulating hormone and phorbol ester on glycosaminoglycan synthesis in porcine thyroid epithelial cells in **primary** culture

AUTHOR(S): Wegrowski, J.; Bellon, G.; Haye, B.; Borel, J. P.

CORPORATE SOURCE: Lab. Biochim., Fac. Med., Reims, 51095, Fr.

SOURCE: Cell Biology International Reports (1989), 13(10), 881-90
CODEN: CBRPDS; ISSN: 0309-1651

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The effects of TSH and of a **tumor** promoter (12-O-tetradecanoyl-phorbol-13-acetate) on glycosaminoglycan (GAG) synthesis were studied in porcine thyroid epithelial cells in **primary** culture. TSH is known to involve a cAMP mechanism and phorbol **ester** to act by the protein kinase C pathway. Chronic treatment of cells with TSH increased the synthesis of heparan sulfate associated with the cell layer and **hyaluronic** acid in the culture medium. Phorbol **ester** increased the radioactivity (from [3H]glucosamine and [35S]sulfate) of total GAGs in the culture medium but had no effect on GAGs associated with the cell layer. It inhibited the pos. effect of TSH on heparan sulfate synthesis. In thyroid epithelial cells, the synthesis of the GAGs associated with the cell layer and those secreted into the culture medium are evidently regulated by different intracellular mechanisms.

L17 ANSWER 11 OF 20 MEDLINE on STN

ACCESSION NUMBER: 2006254340 IN-PROCESS

DOCUMENT NUMBER: PubMed ID: 16573652

TITLE: Translational event mediates differential production of tumor necrosis factor-alpha in hyaluronan-stimulated microglia and macrophages.

AUTHOR: Wang Mei-Jen; Kuo Jon-Son; Lee Wen-Wen; Huang Hsin-Yi; Chen Wu-Fu; Lin Shinn-Zong

CORPORATE SOURCE: Neuro-Medical Scientific Center, Buddhist Tzu-Chi General Hospital, Tzu-Chi College of Technology, Hualien, Taiwan.

SOURCE: Journal of neurochemistry, (2006 May) Vol. 97, No. 3, pp. 857-71. Electronic Publication: 2006-03-29.

Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: NONMEDLINE; IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 9 May 2006
Last Updated on STN: 16 May 2006

AB Recent evidence has demonstrated that **hyaluronan** synthase 2 mRNA is up-regulated after brain ischemia. After a cerebral ischemic event, microglia and macrophages are the major inflammatory cells and are activated by **hyaluronan** (HA). However, it is unclear how these cells compare with regard to HA responsiveness. We show here that peritoneal macrophages and RAW 264.7 macrophages produced more than five- and 10-fold more **tumor** necrosis factor-alpha (TNF-alpha) than **primary** microglia and BV-2 microglia, respectively. Antibody blockade study showed that CD44, Toll-like receptor-4 receptor and the receptor for HA-mediated motility were responsible for HA-induced TNF-alpha release. Furthermore, HA induced higher levels of phosphorylated MAPK in RAW 264.7 cells when compared with BV-2 cells. HA-mediated TNF-alpha production required p38 MAPK, extracellular-regulated kinase and c-Jun N-terminal kinase phosphorylation in both cell types. The levels of HA-induced TNF-alpha mRNA expression in BV-2 cells were only twofold lower compared with RAW 264.7 cells, suggesting that a translational event is involved in the differential production of TNF-alpha. **Western** blot analysis revealed that HA treatment resulted in more rapid phosphorylation of eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) and more effective dissociation of 4E-BP1 from eukaryotic initiation factor 4E in RAW 264.7 cells than in BV-2 cells. Additionally, HA-induced phosphorylation of 4E-BP1 was dependent on MAPK signaling, indicating that RAW 264.7 cells exhibited higher levels of hyperphosphorylated 4E-BP1 possibly due to the overactivation of MAPK. The results suggest that resident microglia and blood-derived monocytes/macrophages exhibit differential sensitivities in response to extracellular mediators after brain ischemia.

L17 ANSWER 12 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2005115084 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15746573
TITLE: Hyaluronic acid butyric esters in cancer therapy.
AUTHOR: Speranza Annalisa; Pellizzaro Cinzia; Coradini Danila
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milan, Italy.
SOURCE: Anti-cancer drugs, (2005 Apr) Vol. 16, No. 4, pp. 373-9.
Ref: 32
Journal code: 9100823. ISSN: 0959-4973.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200507
ENTRY DATE: Entered STN: 5 Mar 2005
Last Updated on STN: 6 Jul 2005
Entered Medline: 5 Jul 2005

AB In this review we focus on a promising novel histone deacetylase (HDAC) inhibitor (HA-But) obtained by the **esterification** of butyric acid (BA), the smallest HDAC inhibitor, with **hyaluronic** acid (HA), the main constituent of the extracellular matrix which selectively recognizes a transmembrane receptor (CD44) overexpressed in most **primary** cancers and associated with **tumor** progression. In vitro, HA-But has proved to be 10-fold more effective than BA in inhibiting the proliferation of a panel of human cancer cell lines, representative of the most common human cancers, and, similar to BA, to

regulate the expression of some cell cycle-related proteins, to induce growth arrest in the G1/G0 phase of the cell cycle and to increase histone acetylation. In vivo, HA-But treatment has demonstrated a marked potency in inhibiting **primary tumor** growth and lung metastases formation from murine Lewis lung carcinoma (LL3) as well as liver metastases formation from intrasplenic implantation of LL3 or B16-F10 murine melanoma cells. In particular, the effect of s.c. and i.p. treatment with HA-But on liver metastases resulted, respectively, in 87 and 100% metastases-free animals, and in a significant prolongation of the survival time compared to the control groups. The results suggest that the presence of the HA backbone does not interfere with the biological activity of butyric residues and that HA-But could represent a promising cell-targetable antineoplastic agent for the treatment of **primary** and metastatic **tumors**.

L17 ANSWER 13 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2004222806 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15122068
TITLE: Hyaluronic-acid butyric esters as promising antineoplastic agents in human lung carcinoma: a preclinical study.
AUTHOR: Coradini Danila; Pellizzaro Cinzia; Abolafio Gabriella; Bosco Marco; Scarlata Ignazio; Cantoni Silvia; Stucchi Luca; Zorzet Sonia; Turrin Claudia; Sava Gianni; Perbellini Alberto; Daidone Maria Grazia
CORPORATE SOURCE: Unit of Biomolecular Determinants in Prognosis and Therapy, Experimental Department, Istituto Nazionale per lo Studio e la Cura dei Tumori, Milano, Italy.. danila.coradini@istitutotumori.mi.it
SOURCE: Investigational new drugs, (2004 Aug) Vol. 22, No. 3, pp. 207-17.
Journal code: 8309330. ISSN: 0167-6997.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200411
ENTRY DATE: Entered STN: 5 May 2004
Last Updated on STN: 19 Dec 2004
Entered Medline: 22 Nov 2004

AB New promising compounds, derived from the **esterification** of **hyaluronic** acid with butyric acid, were investigated in vitro on a non-small cell lung carcinoma cell line (NCI-H460) and an its metastatic subclone (NCI-H460M). All new compounds exerted a dose-dependent inhibitory effect on both cell lines, which expressed CD44, the specific surface receptor for **hyaluronic** acid, in a very high percentage of cells (90%). HE1, the most effective of these compounds, was 10-fold more effective than sodium butyrate (NaB) in inhibiting cell proliferation. Similarly to NaB, after 24 hours of treatment, HE1 affected the expression of three cell cycle-related proteins (p27(kip1), p53 and p21(waf1)) responsible for growth arrest, indicating that the presence of the **hyaluronic** acid backbone does not interfere with the biologic activity. Intratumoral treatment with HE1 demonstrated a marked efficacy on **primary tumor** growth and on lung metastases formation of the murine Lewis Lung Carcinoma model. Altogether, present findings suggest a possible clinical application of these novel butyric pro-drugs in **primary** and metastatic lung cancer.

L17 ANSWER 14 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002466271 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12225794
TITLE: Receptor for hyaluronan acid-mediated motility (RHAMM) is a new immunogenic leukemia-associated antigen in acute and chronic myeloid leukemia.

AUTHOR: Greiner Jochen; Ringhoffer Mark; Taniguchi Masanori; Schmitt Anita; Kirchner Dieter; Krahn Gertraud; Heilmann Volker; Gschwend Jurgen; Bergmann Lothar; Dohner Hartmut; Schmitt Michael
CORPORATE SOURCE: Third Department of Internal Medicine, University of Ulm, Ulm, Germany.
SOURCE: Experimental hematology, (2002 Sep) Vol. 30, No. 9, pp. 1029-35.
Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200211
ENTRY DATE: Entered STN: 13 Sep 2002
Last Updated on STN: 13 Dec 2002
Entered Medline: 8 Nov 2002

AB OBJECTIVE: Identification of leukemia-associated antigens (LAA) eliciting an immune response in patients is a prerequisite for specific immunotherapy of leukemias. To identify new LAA, we used the method of serologic screening of cDNA expression libraries (SEREX). MATERIALS AND METHODS: A SEREX library of the cell line K562 was subjected to allogeneic screening with sera from patients with acute myeloid leukemia (AML) or chronic myeloid leukemia (CML) vs sera from healthy volunteers. RESULTS: The receptor for **hyaluronan** acid-mediated motility (RHAMM) involved in cell growth and metastasis was identified as a new LAA. Serologic responses to RHAMM were observed in patients with AML (42%), CML (31%), melanoma (83%), renal cell carcinoma (40%), breast cancer (67%), and ovarian carcinoma (50%), but not in HV or patients with autoimmune diseases. RHAMM mRNA was detectable in peripheral blood mononuclear cells (PBMN) of 60% of newly diagnosed AML patients. **Western** blotting stained positive for RHAMM protein in 70% of AML patients. mRNA expression of RHAMM also was found in patients with CML (40%), renal cell carcinoma (73%), breast carcinoma (60%), and ovarian carcinoma (50%). In melanoma, RHAMM mRNA expression was detected in metastases (80%) but not in **primary tumors**. RHAMM is differentially expressed: significant mRNA expression was not found in normal tissues, except from testis, placenta, and thymus, or in PBMN- and CD34-separated cell samples of healthy volunteers. CONCLUSIONS: RHAMM is an immunogenic antigen in leukemias and solid **tumors** and might be a potential target structure for cellular immunotherapies and antibody therapies.

L17 ANSWER 15 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2002463778 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12222834
TITLE: The hyaluronan receptor RHAMM/IHABP in astrocytoma cells: expression of a tumor-specific variant and association with microtubules.
AUTHOR: Zhou Rixin; Wu Xiao; Skalli Omar
CORPORATE SOURCE: Department of Cellular Biology and Anatomy, Louisiana State University Medical Center in Shreveport, 71130-39932, USA.
CONTRACT NUMBER: NS-35317 (NINDS)
SOURCE: Journal of neuro-oncology, (2002 Aug) Vol. 59, No. 1, pp. 15-26.
Journal code: 8309335. ISSN: 0167-594X.
PUB. COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 12 Sep 2002
Last Updated on STN: 16 Jan 2003
Entered Medline: 15 Jan 2003

AB **Hyaluronan** binding to its cellular receptors CD44 and ICAM-1

appears to enhance the malignant behavior of **tumors**, including astrocytomas. RHAMM/IHABP, another **hyaluronan** receptor, has been identified in breast carcinoma cells, but its presence in astrocytomas is yet undetermined. Herein, we report that a monoclonal antibody against plectin (a cytoskeletal protein linker) recognizes on **Western** blots of U-373 MG glioblastoma cells, a 300-kDa band corresponding to plectin and two bands of 86 and 70 kDa. cDNA cloning and Northern blotting reveals that these two bands represent isoforms of RHAMM/IHABP. Sequence comparisons suggest that the plectin monoclonal antibody recognizes RHAMM/IHABP because this protein and plectin share short peptide sequences of similar **primary** and secondary structure. **Western** blotting demonstrates that most human astrocytoma tissues and cell lines express the 86- and 70-kDa isoforms of RHAMM/IHABP. Interestingly, the 70-kDa variant is undetectable in normal brain tissues and in **primary** cultures of astrocytes suggesting that its expression is **tumor**-specific. Transfection experiments with epitope-tagged RHAMM/IHABP cDNA established that RHAMM/IHABP associates with microtubules in astrocytoma cells, while in normal astrocytes it either co-localizes with microtubules or has a diffuse cytoplasmic distribution. This suggests that RHAMM/IHABP has the capacity to bind to microtubules in normal and transformed astrocytes, and that neoplasia may favor this association.

L17 ANSWER 16 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2000270195 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10809739
TITLE: Hyaluronan anchoring and regulation on the surface of vascular endothelial cells is mediated through the functionally active form of CD44.
AUTHOR: Nandi A; Estess P; Siegelman M H
CORPORATE SOURCE: Laboratory of Molecular Pathology, Department of Pathology, the University of Texas Southwestern Medical Center, Dallas, Texas 75235-9072, USA.
CONTRACT NUMBER: HL56746 (NHLBI)
R01 CA57571 (NCI)
SOURCE: The Journal of biological chemistry, (2000 May 19) Vol. 275, No. 20, pp. 14939-48.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 29 Jun 2000
Last Updated on STN: 29 Jun 2000
Entered Medline: 21 Jun 2000

AB CD44 on lymphocytes binding to its carbohydrate ligand **hyaluronan** can mediate **primary** adhesion (rolling interactions) of lymphocytes on vascular endothelial cells. This adhesion pathway is utilized in the extravasation of activated T cells from the blood into sites of inflammation and therefore influences patterns of lymphocyte homing and inflammation. **Hyaluronan** is a glycosaminoglycan found in the extracellular matrix and is involved in a number of biological processes. We have shown that the expression of **hyaluronan** on the surface of endothelial cells is inducible by proinflammatory cytokines. However, the manner through which **hyaluronan** is anchored to the endothelial cell surface so that it can resist shear forces and the mechanism of the regulation of the level of **hyaluronan** on the cell surface has not been investigated. In order to characterize potential **hyaluronan** receptors on endothelial cells, we performed analyses of cell surface staining by flow cytometry on intact endothelial cells and ligand blotting assays using membrane fractions. **Hyaluronan** binding activity was detected as a major species corresponding to the size of CD44, and this was confirmed

to be the same by **Western** blotting and immunoprecipitation. Moreover, alterations in the surface level of **hyaluronan** after **tumor** necrosis factor-alpha stimulation is regulated **primarily** by changes in the cell surface levels of the **hyaluronan**-binding form of CD44. In laminar flow assays, lymphoid cells specifically roll on **hyaluronan** anchored by purified CD44 coated on glass tubes, indicating that the avidity of the endothelial CD44/**hyaluronan** interaction is sufficient to support rolling adhesions under conditions mimicking physiologic shear forces. Together these studies show that CD44 serves to anchor **hyaluronan** on endothelial cell surfaces, that activation of CD44 is a major regulator of endothelial surface **hyaluronan** expression, and that the non-covalent interaction between CD44 and **hyaluronan** is sufficient to provide resistance to shear under physiologic conditions and thereby support the initial steps of lymphocyte extravasation.

L17 ANSWER 17 OF 20 MEDLINE on STN
ACCESSION NUMBER: 2000179901 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10713114
TITLE: Heparan sulfate proteoglycan isoforms of the CD44 hyaluronan receptor induced in human inflammatory macrophages can function as paracrine regulators of fibroblast growth factor action.
AUTHOR: Jones M; Tussey L; Athanasou N; Jackson D G
CORPORATE SOURCE: Department of Cellular Science, John Radcliffe Hospital, Headington, Oxford OX3 9DU, United Kingdom.
SOURCE: The Journal of biological chemistry, (2000 Mar 17) Vol. 275, No. 11, pp. 7964-74.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 21 Apr 2000
Last Updated on STN: 21 Apr 2000
Entered Medline: 12 Apr 2000

AB The CD44 glycoprotein is expressed in multiple isoforms on a variety of cell types where it functions as a receptor for **hyaluronan** -mediated motility. Recently, interest has centered on CD44 heparan sulfate proteoglycan (HSPG) isoforms because of their potential to **sequester** heparin-binding growth factors and chemokines. Expression of these isoforms on ectodermal cells has recently been shown to regulate limb morphogenesis via presentation of fibroblast growth factor (FGF) 4/FGF 8 while expression on **tumor** cells was shown to **sequester** hepatocyte growth factor and promote **tumor** dissemination. To date, however, CD44 HSPG expression in tissue macrophages and lymphocytes has not been adequately investigated, despite the fact these cells actively synthesize growth factors and chemokines and indirect evidence that monocyte CD44 **sequesters** macrophage inflammatory protein-1beta. Here we show **primary** human monocytes rather than lymphocytes express CD44 HSPGs, but only following in vitro differentiation to macrophages or activation with the proinflammatory cytokine interleukin-1alpha or bacterial lipopolysaccharide. Furthermore, we show these isoforms are preferentially modified with heparan rather than chondroitin sulfate, bind the macrophage-derived growth factors FGF-2, vascular endothelial growth factor, and heparin-binding epidermal growth factor with varying affinities (K(d) 25-330 nM) and in the case of FGF-2, can stimulate productive binding to the high affinity tyrosine kinase FGF receptor 1 (FGFR1). In contrast, we find no evidence for significant binding to C-C chemokines. Last, we confirm by immunofluorescent antibody staining that inflamed synovial membrane macrophages express CD44 HSPGs and that expression is greatest in cells containing high FGF-2 levels. These

results suggest a paracrine role for macrophage CD44 HSPG isoforms in the regulation of growth factor action during inflammation.

L17 ANSWER 18 OF 20 MEDLINE on STN
ACCESSION NUMBER: 96025120 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7574929
TITLE: Restoration of CD44H expression in colon carcinomas reduces tumorigenicity.
AUTHOR: Tanabe K K; Stamenkovic I; Cutler M; Takahashi K
CORPORATE SOURCE: Department of Surgery, Massachusetts General Hospital, Boston, USA.
CONTRACT NUMBER: CA55735 (NCI)
CA64454 (NCI)
DK 43351 (NIDDK)
SOURCE: Annals of surgery, (1995 Oct) Vol. 222, No. 4, pp. 493-501; discussion 501-3.
Journal code: 0372354. ISSN: 0003-4932.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199511
ENTRY DATE: Entered STN: 27 Dec 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 22 Nov 1995
AB OBJECTIVE: The functional consequences of reintroduction of the CD44H cell adhesion molecule into colon carcinomas were investigated. BACKGROUND: CD44 is a cell surface adhesion molecule that is normally present in numerous isoforms as a result of messenger RNA alternative splicing. Individual CD44 isoforms differ in their ability to enhance **tumorigenic** or metastatic potential when overexpressed on **tumor** cells. Reverse transcriptase-polymerase chain reaction analysis demonstrates that CD44H is down-regulated during transformation of normal colon mucosa to carcinoma. The functional consequences of CD44H down-regulation in colon carcinomas has not been clarified. METHODS: **Tumor** cell lines and fresh tissue specimens were examined for CD44 expression by **Western** blot analysis. CD44H cDNA and site-directed mutants of CD44H cDNA were transfected into colon carcinoma cells. Stable transfectants were examined for adhesion to **hyaluronate**, in vitro growth, and in vivo growth. RESULTS: CD44H expression was nearly undetectable in **primary** colon carcinomas and colon carcinoma cell lines. In contrast, normal mucosa expressed high levels of CD44H. When CD44H was reintroduced into colon carcinoma cells, their in vitro and in vivo growth was significantly reduced. This CD44H-mediated growth rate reduction required an intact cytoplasmic domain. CONCLUSIONS: Transformation of normal mucosa to colon carcinoma is associated with a down-regulation of CD44H, which consequently may enhance the growth rate and **tumorigenicity**.

L17 ANSWER 19 OF 20 MEDLINE on STN
ACCESSION NUMBER: 95012201 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7523275
TITLE: Expression of the cell adhesion molecule CD44 in gastric adenocarcinomas.
AUTHOR: Washington K; Gottfried M R; Telen M J
CORPORATE SOURCE: Department of Pathology, Duke University Medical Center, Durham, NC 27710.
CONTRACT NUMBER: HL 02233 (NHLBI)
HL 33572 (NHLBI)
SOURCE: Human pathology, (1994 Oct) Vol. 25, No. 10, pp. 1043-9.
Journal code: 9421547. ISSN: 0046-8177.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English

FILE SEGMENT: Priority Journals
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AB CD44, an integral membrane glycoprotein expressed by many cell types, serves as the principal transmembrane **hyaluronate** receptor and may be a determinant of metastatic and invasive behavior in carcinomas. The expression of CD44 in 23 gastric adenocarcinoma and 12 peptic ulcer disease (PUD) resection specimens and gastric carcinoma cell lines HS746t and KATO III was examined by immunohistochemistry using the murine monoclonal antibody A3D8 on formalin-fixed, paraffin-embedded tissue or cells. **Western** blot analysis of whole cell lysates of KATO III and HS746t cells showed protein bands at 85 to 90 kd with KATO III cells expressing an additional band at 145 kd. In normal stomach gastric epithelium was negative. In PUD foveolar epithelium was focally positive, but staining did not correlate with the extent of gastritis. In carcinoma cases intensity of staining was progressively stronger comparing intestinal metaplasia with dysplasia with intramucosal carcinoma. Invasive carcinoma was invariably more strongly positive than dysplasia or intramucosal carcinoma. Twelve adenocarcinomas were weakly positive and 11 were strongly positive. The staining intensity of metastases (12 cases) was the same or weaker than the **primary tumor**. For the 12 patients whose carcinomas were weakly positive, mean length of survival for the six who died was 23.3 months. Five of the 11 patients whose carcinomas strongly expressed CD44 died within the study period with a mean length of survival of 11.0 months. A key consequence of CD44 overexpression in gastric carcinomas may be development of the invasive phenotype and strong expression may indicate a poorer prognosis.

L17 ANSWER 20 OF 20 MEDLINE on STN
ACCESSION NUMBER: 90030452 MEDLINE
DOCUMENT NUMBER: PubMed ID: 2805078
TITLE: Effects of thyroid-stimulating hormone and phorbol ester on glycosaminoglycan synthesis in porcine thyroid epithelial cells in **primary** culture.
AUTHOR: Wegrowski J; Bellon G; Haye B; Borel J P
CORPORATE SOURCE: Laboratoire de Biochimie, UA CNRS 610, Faculte de Medecine, Reims, France.
SOURCE: Cell biology international reports, (1989 Oct) Vol. 13, No. 10, pp. 881-90.
Journal code: 7708050. ISSN: 0309-1651.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198912
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AB The effects of thyroid-stimulating hormone (TSH) and a **tumor** promoter: 12-0-tetradecanoyl-phorbol-13-acetate on glycosaminoglycan (GAG) synthesis were studied in porcine thyroid epithelial cells in **primary** culture. TSH is known to involve cyclic AMP mechanism and phorbol **ester** to act by protein kinase C pathway. Chronic treatment of cells with TSH increased the synthesis of heparan sulphate associated with the cell layer and **hyaluronic** acid in the culture medium. Phorbol **ester** increased the radioactivity of total GAGs in the culture medium but had no effect on GAGs associated with the cell layer. It inhibited the positive effect of TSH on heparan sulphate synthesis. These results suggest that in thyroid epithelial cells the synthesis of the GAGs associated with the cell layer and those secreted into the culture medium are regulated by different intracellular mechanisms.